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Desymmetrization of Cyclopropenes via the Potassium-Templated Diastereoselective 7-*exo*-*trig* Cycloaddition of Tethered Amino Alcohols toward Enantiopure Cyclopropane-Fused Oxazepanones with Antimycobacterial Activity

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Abstract

A strain-release-driven, cation-templated intramolecular nucleophilic addition of tethered alkoxides to prochiral cyclopropenes is described. Employment of chiral β- and γ-amino alkoxides allowed for highly diastereoselective assembly of a small series of enantiopure cyclopropane-fused oxazepanones. It was shown that the chiral center at C-4 plays a crucial role in controlling desymmetrization of the cyclopropenyl moiety, instigated by a profound potassium-templated effect. The preliminary biological activities of the new cyclopropane-fused medium heterocycles against Gram-positive bacteria, Gram-negative bacteria, mycobacteria, cancer cells, and fungus were evaluated.

Graphical Abstract

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[‖]Author Contributions

V. A. Maslivetc and D. N. Turner contributed equally.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00640.

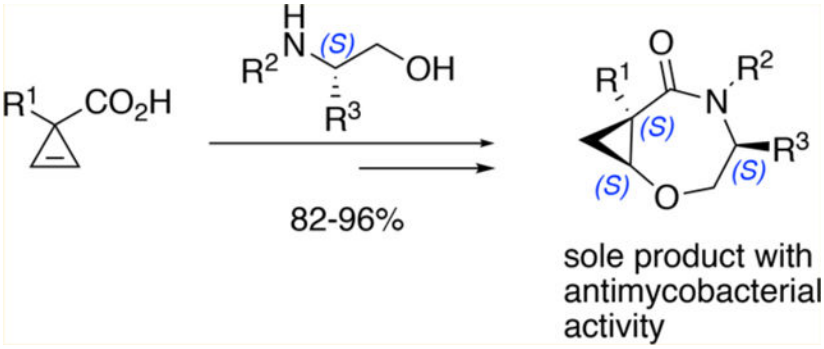
Spectral data (PDF)

X-ray crystallography data for C20H19Cl2NO (CIF)

X-ray crystallography data for C11 H10 N O (CIF)

X-ray crystallography data for C11 H10 N O (CIF)

The authors declare no competing financial interest.



INTRODUCTION

Advances in base-assisted additions of heteroatom-based nucleophiles to cyclopropenes made available novel stereo-defined cyclopropyl scaffolds,[1] possessing oxygen,[2] nitrogen,[3] sulfur,[4] or halogen[5] entities, that complement transition-metal-catalyzed cyclopropanation methodologies.[6,7] Both intermolecular (Scheme 1, eq 1) and intramolecular (Scheme 1, eq 2) addition of tethered nucleophiles, employing carbon-[8] or oxygen-based species, has been reported.[9,10] In all these studies achiral tethered nucleophilic entities were used for cyclizations affording racemic products. A diastereoselective 8-*endo-trig* cycloaddition using chiral cyclopropene precursor 8 has been demonstrated (Scheme 1, eq 3),[10] while a complementary approach involving intramolecular nucleophilic addition of tethered chiral alkoxides to prochiral cyclopropene moieties has not been fully explored. To date, only two examples were communicated by our group,[11] using cyclopropene **11** generated in situ via 1,2-elimination of bromocyclopropane **10** (Scheme 2). The limited availability of chiral precursors **10** warranted further studies to adapt this methodology to more stable, isolable cyclopropenes accessible via the metal-catalyzed cyclopropenation reactions.[12] Herein, we report the development of a synthetic approach that allows for modular assembly of chiral medium-sized heterocycles **6** and **12** bearing a fused cyclopropane moiety. It should be pointed out that fused oxazepines are a very important class of biologically active molecules that display diverse pharmacological activities.[1] Known bioactivities for this class of compounds include anticonvulsant, antimicrobial, anticancer, and antipsychotic agents and calcium antagonists and neuroprotectors. Development of new approaches to these important molecules, especially stereoselective, can lead to the discovery of new privilege medicinal structures. Preliminary biological studies of our new scaffolds revealed several hits showing promising antimicrobial activity against *Mycobacterium abscessus*,[13] a rapid-growing highly virulent chemotherapy-resistant mycobacterial pathogen.

RESULTS AND DISCUSSION

We have recently communicated an efficient synthesis of medium cyclic ethers **6** via a formal nucleophilic cyclization of bromocyclopropanes **4** (Scheme 1, eq 2),[9a] involving an *in situ* base-assisted generation of reactive cyclopropene **5**, which, once formed, is immediately trapped by a tethered alkoxide. Our computational studies suggested that the mechanism of this strain-release-driven reaction involves a transition state where the potassium ion is coordinated to both alkoxide and amide oxygens, as well as to the carbon

atom bearing a partial negative charge (C-8) (TS1 in Scheme 6). It was expected and confirmed experimentally that the templating effect induced constraints on the rotors in the tether, making the cyclization pathway more favorable vis-a-vis oligo- and polymerization. Furthermore, the rigidity of such activated complexes allowed for high diastereoselectivity of the newly formed stereogenic centers when chiral amino alcohol-tethered prochiral cyclopropenes are used as substrates. In our preliminary communication,[11] we have demonstrated two examples of such cyclization of bromocyclopropanes **10** decorated with (*R*)-phenylglycinol (R^3 = Ph, R^4 = H) and (*R,R*)-pseudoephedrine (R^3 = Me, R^4 = Ph) side chains. Highly stereoselective formation of bicyclic products **12** was observed in both cases, while diastereomers **13** were never detected.

Further exploration of this approach has met with synthetic challenges and was essentially unrewarded. Numerous experimentations proved that only 1-methyl-2-bromocyclopropane carboxylic acid is fairly suitable for the preparation of starting amides **10** (R^1 = Me).[14] *In situ* generation of cyclopropenyl amides **11** via 1,2-dehydrohalogenation using analogues of **10** with $R^1 \neq$ Me has severe limitations rendering this synthetic pathway impractical. Accordingly, we embarked on an alternative route to cyclopropenyl amides **11**, via the Rh(II)-catalyzed [2 + 1]-cycloaddition of diazoacetates with trimethylsilylacetylene,[15] which was improved and tailored to our systems.[16] This approach was benchmarked on racemic cyclopropene amides derived from achiral amino alcohols. To this end, available 1-arylcycloprop-2-ene-1-carboxylic acids[15,16] **14** were derivatized with *N*-protected 2-aminoethanols and 3-aminopropanols **15** to afford the corresponding amides **16**, which were used crude in the subsequent base-assisted cyclization (Scheme 3). We first probed the cyclization of amide **16aa**, which reacted uneventfully affording oxazabicyclo[5.1.0]octanone **17aa** as a sole product in good yield (Figure 1). Note that 18-crown-6 ether was not used in this case, as compared to the earlier examples depicted in Scheme 1 and 2,[9–11] as this catalyst is required only in the 1,2-dehydrobromination step for efficient generation of cyclopropene. With the positive initial results in hand, we moved on to evaluate the effect of substituents at nitrogen (R^2) and sp^3-hybridized carbon of cyclopropene (R^1) on the cyclization propensity of cyclopropenylamides. We were pleased to see that *N*-methyl (**17ab, 17bb, 17cb**) and various *N*-benzyl 2-oxa-5-azabicyclo[5.1.0]octan-6-ones (**17ac, 17ad, 17af, 17ba, 17ca**) were efficiently obtained via this approach (Figure 1). *N*-Phenyl derivative **17af** was produced only in poor yield, which was attributed to a facile base-assisted hydrolysis of the C−N bond in anilides, as noted previously.[14] This side reaction is suppressed in electron-rich anilides, so cyclization of *p*-anisidine derivatives proceeded smoother, affording better yields of oxazepanones **17ag** and **17bg** (Figure 1). Tethered 3-aminopropanols underwent 8-*exo-trig* cyclization efficiently under the same reaction conditions to give oxazocanones **17ah, 17bh, 17bi**, and **17ch** (Figure 1).

Having mapped the substrate scope, we next investigated the possibility of a diastereoselective nucleophilic 7-*exo-trig* cyclization of tethered chiral alkoxides with prochiral cyclopropenes.[17] The two-carbon-atom tether allows for independent installation of two stereogenic centers, which gives rise to four different modes depicted in Scheme 4. Thus, derivatives of chiral amino ethanols with (*S*)-configuration at C-2 (**18**) can potentially

produce two products: (1*S*,4*S*,7*S*)-**19** or (1*R*,4*S*,7*R*)-**20** (mode **I**). Likewise, (**R**)-configuration at C-1 in the amino alcohol tether of **21** would give rise to diastereomers (1*S*,3*R*,7*S*)-**22** or (1*R*,3*R*,7*R*)-**23**, respectively (mode **II**). Two additional modes are possible when the diastereoselectivity is induced in the presence of two contiguous chiral centers at C-1 and C-2 of the amino alcohol tether. Thus, *threo*-(**24**) could potentially afford products (1*S*,3*S*,4*S*,7*S*)-**25** or (1*R*,3*S*,4*S*,7*R*)-**26** (mode **III**), while *erythro*-(**27**) could provide (1*S*,3*R*,4*S*,7*S*)-**28** and (1*R*,3*R*,4*S*,7*R*)-**29**, respectively (mode **IV**) (Scheme 4). The following discussion addresses all the above-mentioned cyclization modes in detail.

To probe mode **I**, a set of condensation reactions between 1-arylcycloprop-2-ene-1-carboxylic acids (**14a−c**) and chiral amino alcohols **30b−d** were carried out, and thus obtained chiral cyclopropenes **18** were used crude in the cyclization (Scheme 5) under the standard reaction conditions described above (Scheme 3). We were very pleased to find that, in all cases, the enantiomerically pure (3*S*,6*S*,7*S*)-2-oxa-5-azabicyclo-[5.1.0]-octan-6-ones **19** were obtained as sole products (3*R*,6*R*,7*R* enantiomer was obtained for **19bc**, originated from (*R*)-phenylglycinol). None of these reactions produced any detectable amounts of the diastereomers **20** (Figure 2). The relative and absolute configuration of compound 19bd was unambiguously confirmed by single-crystal X-ray crystallography.[18]

Our rationale for the origins of the high diastereoselectivity obtained in cyclization mode **I** is shown in Scheme 6. Our earlier computational studies performed on achiral models suggested that the transition state in 7-*exo*-*trig* cyclization (**TS1**) has a very rigid pseudoboat conformation, stabilized by a three-center coordinated potassium cation bound through the alkoxide and carbonyl oxygens as well as the anionic carbon atom.[9a] Assuming the same transition state model is realized for the chiral substrates in the present studies, a nucleophilic attack at the now diastereotopic C-7 or C-8 would result in two nonequivalent reaction pathways ***a*** and ***b***, respectively (Scheme 6). Path ***a***, affording product **19**, operates via a lower-energy transition state **TS2a**, in which substituent R^3 at C-4 assumes the thermodynamically more favored, pseudoequatorial (bowsprit) conformation. The alternative, higher-energy transition state **TS2b**, resulting from nucleophilic attack ***b***, forces the R^3 group into a pseudoaxial (flagpole) position where it experiences a strong *syn*-pentane interaction with hydrogen at C-8, which disfavors formation of product **20**.

To test mode **II**, (*R*)-2-(benzylamino)-1-phenylethan-1-ol (**31**) was condensed with cyclopropenylcarboxylic acid **14b**, and the resulting amide **21b** was subjected to the base-assisted cyclization. A 1:4 ratio of two isomeric products, **22b** and **23b**, was obtained (Scheme 7). Configurations of both products were unambiguously assigned by 2D NOESY experiments.[18] A mechanistic scenario consistent with the observed marginal diastereoselectivity is outlined in Scheme 8. It is believed that the unfavorable 1,3-diaxial interaction between substituent R^4 at C-5 and the R^2 group at nitrogen in the seven-membered complex **TS3a** (resulting from path ***a***) is not as prohibitive as in cyclohexyl analogues. As a result, **22** is produced as a minor product. An alternative, major pathway **b** proceeding via transition state **TS3b**, in which substituent R^4 at the stereogenic center is free of the unfavorable interactions, gives rise to major product **23** (Scheme 8).

Next, we tested modes **III** and **IV** on cyclopropenyl carboxamide derivatives prepared from cyclopropene carboxylic acids 14a−d and (+)- or (−)-pseudoephedrine (**32** or *ent*-**32**) and (−)-ephedrine (**33**). Cyclization of these substrates provided oxazepanones **25** (or *ent*-**25**) and **28**, respectively, as sole products in excellent yields (Scheme 9, Figure 3). Single-crystal X-ray diffraction analysis unambiguously con-firmed the absolute configurations of products **25c** and **28c**.[18] The origins of high diastereoselectivity in the 7-*exo*-*trig* nucleophilic cyclization producing 25 (mode **III**) are analyzed in Scheme 10. It is believed that the nucleophilic attack at C-7 (path ***a***) is highly preferred due to a more favored transition state **TS4a**, in which both substituents R^3 and R^4 occupy a pseudoequatorial position. A complementary path **b** would lead to a much more energetic transition state **TS4b**, in which substituent R^3 in a flagpole orientation is experiencing steric repulsions with hydrogen at C-8 (Scheme 10), similar to that described above for mode I (Scheme 6). The 1,3-diaxial interaction between substituents R^2 and R^4 could be another contributing factor to destabilization of **TS4b**. This effect, however, is not expected to be significant for small N-substituents, such as a methyl group.

Finally, the high selectivity observed in cyclization mode **IV** is rationalized as follows (Scheme 11). Transition state **TS5a** resulting from the nucleophilic attack at C-7 (path ***a***) is rather favorable, since the 1,3-diaxial interaction between substituents R^2 and R^4, as was stated above, is quite insignificant for nonbulky R^2 groups. The alternative transition state **TS5b**, resulting from an attack at C-8 (path ***b***), experiences prohibitive steric interactions with a flagpole substituent R^3 (Scheme 11). Arguably, in all four cyclization modes analyzed above, the stereoselectivity is greatly influenced by configuration of the stereogenic center at C-4 and the R^3 group, while the C-5 substituent R^4 plays a modest role, at least for derivatives with a nonencumbered substituent on the nitrogen. The strong cation-templating effect elicits conformational rigidity of the transition state and amplifies the asymmetric induction arising from a rather remote chiral center, which ultimately allows for the efficient desymmetrization of the cyclopropenyl moiety.

The obtained enantiopure 2-oxa-5-azabicyclo[5.1.0]octan-6-ones constitute very attractive biological probes as this unique heterocyclic scaffold just recently emerged on the chemical space map. Accordingly, we performed a preliminary biological evaluation of a few representative compounds for antimicrobial and anticancer activities. The antiproliferative activity was assessed by using the cancer cell line, HeLa, as a model for human cervical adenocarcinoma, through the measurements of mitochondrial dehydrogenase activities using the MTT method.[19] In addition, the synthesized compounds were tested against *Staphylococus epidermidis* (ATCC 75984) and *Escherichia coli* (ATCC 25922), where minimum inhibitory concentrations (MICs) were determined by the broth micro-dilution method using MTT assay.[20] Since the described compounds bear some similarity with azepines known to possess activity against mycobacteria,[21] we also tested products 19, 25, and 28 against *Mycobacterium abscessus* (ATCC 19977) by MTT assay. The potency of synthesized compounds against yeasts was also evaluated using *Candida albicans* (ATCC 26555).

Our preliminary tests revealed that none of these compounds demonstrated any activity against *Candida albicans*, *Staphylococus epidermidis*, or *Escherichia coli* up to 100 μM nor

significant cytotoxicity on HeLa cells. However, promising activity against *Mycobacterium abscessus* was observed for selected 2-oxa-5-azabicyclo[5.1.0]octan-6-ones (Table 1). The latter finding, coupled with apparent low general toxicity against cultured human cells, set the grounds for further SAR studies.

CONCLUSION

A potassium-templated, intramolecular nucleophilic addition of alkoxides to isolable, prochiral cyclopropenes has been developed. The scope of this cyclization and the mechanism of enantiomeric induction were investigated on a series of tethered chiral alkoxides. Three out of four tested chiral cyclization modes provided a highly efficient asymmetric induction, governed by the chiral center at C-4 and controlled by the strong chelating effect of potassium. The obtained optically active 2-oxa-5-azabicyclo[5.1.0]octan-6-ones were tested against representative mycobacterial infection-causing organisms as well as other bacteria, pathogenic fungi, and human cultured cell lines. The biological profile exhibited by some of these unique chiral cyclopropane-fused medium-sized heterocycles is noteworthy and is currently being further explored in our laboratories.

EXPERIMENTAL SECTION

General.

NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) with a dual carbon/proton cryoprobe (CPDUL), Bruker III (400 MHz) equipped with BBO probe. ^{13}C NMR spectra were registered with broadband decoupling. The (+) and (−) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. IR spectra were recorded on a ThermoFisher Nicolet iS 5 FT-IR spectrometer. HRMS was carried out on an LCT Premier (Micromass Technologies) instrument employing ESI TOF detection techniques. Glassware used in moisture-free syntheses was flame-dried in a vacuum prior to use. Column chromatography was carried out on silica gel (Sorbent Technologies, 40−63 mm). Precoated silica gel plates (Sorbent Technologies Silica XG 200 mm) were used for TLC analyses. Anhydrous dichloromethane was obtained by passing degassed commercially available HPLC-grade inhibitor-free solvent consecutively through two columns filled with activated alumina and stored over molecular sieves under nitrogen. Water was purified by dual-stage deionization followed by dual-stage reverse osmosis. Anhydrous THF was obtained by refluxing commercially available solvent over calcium hydride followed by distillation in a stream of dry nitrogen. 1-Phenylcycloprop-2-ene-1-carboxylic acid (**14a**),[22] 1-(4-fluorophenyl)-cycloprop-2-ene-1-carboxylic acid (**14b**),[6d] and (S)-2-(benzylamino)-4-methylpentan-1-ol (30d)[23] were synthesized according to the previously published procedures and had physical and spectral properties identical to those earlier reported. Syntheses of 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**14c**), 1-(naphthalen-1-yl)cycloprop-2-ene-1-carboxylic acid (**14d**), and 2-((5-bromo-2-fluorobenzyl)amino)ethan-1-ol (**15e**) are described herein.[18] All other reagents and solvents were purchased from commercial vendors and used as received. See Supporting Information for the spectral charts and X-ray crystallography data.

Biological Studies: Materials and Methods.

All culture cell lines were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA).

Cell Culture.—HeLa cells were cultured in DMEM supplemented with 10% fetal bovine serum (FBS). To evaluate antiproliferative properties of the synthesized compounds, the cells were trypsinized and seeded at 4×10^3 cells per well into 96-well microtiter plates. The cells were grown for 24 h before treatment.

Fungal Culture.—*Candida albicans* (ATCC 26555) was grown overnight in Difco YM Broth at 37 °C in a shaking incubator.

Bacterial Cultures.—*Mycobacterium abscessus* (ATCC 19977) was inoculated in Middlebrook 7H9 medium supplemented with 1% ADC enrichment and incubted at 37 °C in T25 tissue culture flasks for 72 h. *Staphylococus epidermidis and Escherichia coli* were incubated in Tryptic Soy Broth (TSB) for 6 h at 37 °C.

MTT Assay for HeLa (ATCC CCL-2).—All compounds were dissolved in DMSO at a concentration of either 100 or 50 mM prior to cell treatment. The cells were treated at concentrations ranging from 0.004 to 100 μM and incubated for 48 h in 200 μL of media. An amount of 20 μL of MTT reagent in serum-free medium (5 mg/mL) was added to each well and incubated further for 2 h. Media was removed, and the resulting formazan crystals were solubilized in 100 μL of DMSO. A490 was measured using a Thermomax Molecular Device plate reader. The experiments were performed in quadruplicate and repeated at least twice for each compound per cell line. Cells treated with 0.1% DMSO were used as a vehicle control, and phenyl arsine oxide (PAO) was used as a positive killing control.

MTT Assay for Candida albicans (ATCC 26555).—Cells were diluted 1:20 in YM Broth. 2-Fold serial dilutions were prepared as follows: 1000 μL of cells was added to the first well of each 24-well plate, and 500 μL of cells was added to the proceeding wells. Compounds were added at a final concentration of 100 μM. 2-Fold dilutions were continued across all remaining wells. Cells were incubated for 24 h at 37 °C and then treated with 100 μL of MTT (5 mg/mL) and incubated for 3 h. An equal volume of premixed solution of 50% dimethylformamide with 20% sodium dodecyl sulfate (solubilization solution) was added to dissolve the formazan crystals and incubated further for 15 min. The experiments were performed in triplicate. Amphotericin B was used as positive kill control, and untreated cells served as negative controls.

MTT Assay for Staphylococus epidermidis (ATCC 35984) and Escherichia coli (ATCC 25922).—An overnight cell growth was diluted to an optical density of 0.100 at A595; cells were further diluted 1:100 in TSB. An amount of 1000 μL of the dilution was added to each well of a 12-well plate (except the first well, which received only TSB). Each well received one compound at a final concentration of 100 μM. Plates were incubated for 24 h at 37 °C. Cells were subsequently treated with 100 μL of MTT (5 mg/mL) and incubated at 37 °C for 15 min. Solubilization solution was added to dissolve the formazan

crystals and incubated further for 15 min. An amount of 50 μg/mL of colistin (PME) was used as a positive kill control for E. coli; 50 μg/mL of vancomycin was used as a positive kill control for S. *epidermidis*; and untreated cells served as negative controls. The experiments were performed in triplicate.

MTT Assay for Mycobacterium abscessus (ATCC 19977).—Approximately 5.5 × 10^5 mycobacteria per mL or a dilution of 1:500 from an overnight growth were plated at a final volume of 400 μL/well in 48-well plates. Compounds were initially screened at a concentration of 100 μM on *M. abscessus*. Compounds with antimycobacterial activity at 100 μM were screened for further activity by adding the selected compounds to cells at a concentration of 50 μM and 2-fold serially diluting. The plates were incubated in a shaking incubator for 48 h at 37 °C. Following the incubation, 40 μL or 10% w/v of MTT reagent (5 mg/mL) was added to each of the wells. The plates were incubated for 2 h at 37 °C. An amount of 650 μL of solubilization solution was added to each of the wells, and the plate was incubated at 37 °C for an additional 12 h. An amount of 100 μL from each well was transferred into a clear 96-well microtiter plate, and A595 was read in a Thermomax Molecular Device plate reader. Wells containing Middlebrook 7H9 medium and nontreated cells served as negative controls, and a well containing 10 μM PAO-treated cells served as a positive kill control. The experiments were performed in triplicate.

Synthesis of Starting Materials.

1-(2,4-Dichlorophenyl)-cycloprop-2-ene-1-carboxylic Acid (14c).—Solution methyl 1-(2,4-dichlorophenyl)-2-(trimethylsilyl)cycloprop-2-ene-1-carboxylate[9b] (3.71 g, 11.77 mmol, 1.00 equiv) in a mixture of methanol and THF (1:1, 100 mL) was stirred at 0 °C. A 1.5 M aqueous solution of NaOH (102 mL, 153.0 mmol, 13.0 equiv) was added dropwise, and the mixture was stirred for 18 h. Organic solvents were then removed under vacuum, and the remaining aqueous solution was washed with dichloromethane (3 × 50 mL). The remaining aqueous phase was acidified with 1 N aqueous HCl to pH 2 and extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The product was isolated as a colorless solid (Rf 0.27, mp 194−195 °C) by column chromatography eluting with a hexane/EtOAc mixture (2:1). Yield 2.10 g (9.16 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.88 (s, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.28 (s, 2H), 7.19 (dd, J = 8.2, 2.1 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 180.9, 137.9, 135.9, 133.9, 131.2 (+), 129.4 (+), 127.5 (+), 108.0 (+, 2C), 29.4. FTIR (NaCl, cm^{-1}): 3155 (br), 1697. HRMS (TOF ES): found 226.9671, calculated for $C_{10}H_5Cl_2O_2$ $(M - H)^-$ 226.9667 (1.8ppm).

1-(Naphthalen-1-yl)cycloprop-2-ene-1-carboxylic acid (14d).—This compound was synthesized starting from 1-(naphthalen-1-yl)-2-(trimethylsilyl)cycloprop-2-ene-1-carboxylate[9b] (3.82 g, 12.9 mmol, 1.00 equiv) according to the procedure described above for preparation of acid **14c**. The titled product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f 0.27, mp 144−145 °C). Yield 2.23 g (10.6 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.42 (br. s, 1H), 8.08 (d, J =8.3 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.55− 7.46 (m, 2H), 7.45 (s, 2H), 7.41 (t, J = 7.7 Hz, 1H), 7.34 (d, J = 6.9 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ

181.9, 138.1, 133.9, 132.0, 128.9 (+), 128.2 (+), 126.3 (+), 126.0 (+), 125.9 (+), 125.8 (+), 124.3 (+), 108.8 (+, 2C), 29.1. FTIR (NaCl, cm^{-1}): 3162 (br), 1691. HRMS (TOF ES): found 209.0593, calculated for $C_{14}H_9O_2$ $(M-H)^-$ 209.0603 (4.8 ppm).

2-((5-Bromo-2-fluorobenzyl)amino)ethan-1-ol (15e).—5-Bromo-2-fluorobenzaldehyde (2 mL, 3.42 g, 16.8 mmol, 1.0 equiv), 2-aminoethan-1-ol (1.12 mL, 1.13 g, 18.5 mmol, 1.1 equiv), and 30 mL of anhydrous methanol were combined and stirred at RT overnight. The reaction mixture was cooled to 0 °C; $NaBH_4$ (955 mg, 25.3 mmol, 1.5 equiv) was added in portions; and the reaction mixture was stirred for 2 h at RT. The reaction mixture was concentrated in vacuum and partitioned between 10 mL of water and 10 mL of dichloromethane. The aqueous phase was then extracted with dichloromethane (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated to yield the title compound as a colorless solid (mp 75−76 °C). Yield 3.34 g (13.5 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, J = 6.6, 2.5 Hz, 1H), 7.38−7.31 (m, 1H), 6.98−6.88 (m, 1H), 3.83 (s, 3H), 3.70−3.64 (m, 2H), 2.83−2.76 (m, 2H), 1.95 (br. s, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.3 (d, J = 246.1 Hz), 133.1 (d, J = 5.0 Hz, +), 131.7 (d, J = 8.2 Hz, +), 129.5 (d, J = 16.4 Hz), 117.3 (d, J = 23.6 Hz, +), 116.8 (d, J = 3.6 Hz), 61.1 (−), 50.4 (−), 46.6 (d, J = 2.7 Hz, −). FTIR (NaCl, cm^{-1}): 3320 (br), 1236, 1171. HRMS (TOF ES): found 248.0092, calculated for $C_9H_{12}BrFNO$ (M + H) 248.0086 (2.4 ppm).

Cyclization of Achiral Substrates.

5-Benzyl-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (17aa).—*Typical Procedure*. A flame-dried round-bottom flask was charged with 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (500 mg, 3.12 mmol, 1.0 equiv), DMF (2 drops), and freshly distilled anhydrous dichloromethane (7 mL) under nitrogen atmosphere. Oxalyl chloride (400 μL, 592 mg, 4.68 mmol, 1.5 equiv) was then added dropwise, and the mixture was stirred at room temperature for 2 h. The solution was concentrated in a stream of nitrogen; the residue was subjected to a high vacuum, dissolved in anhydrous dichloromethane (2.0 mL), and added dropwise to a stirred solution of 2-(benzylamino)ethan-1-ol (**15a**) (708 mg, 4.68 mmol, 1.5 equiv) and triethylamine (1.3 mL, 948 mg, 9.36 mmol, 3.0 equiv) in anhydrous dichloromethane (3.0 mL). The reaction mixture was stirred at room temperature for 18 h and then partitioned between water (15 mL) and dichloromethane (20 mL). The aqueous phase was acidified with 5 mL of 2 N HCl. The organic phase was then washed with 2 N HCl (3 × 10 mL). The combined aqueous layers were back-extracted once with 10 mL of dichloromethane, which was combined with other organic phases, washed with brine, dried with $MgSO_4$, filtered, and concentrated. The product, *N*-benzyl-*N*-(2-hydroxyethyl)-1-phenylcycloprop-2-ene-1-carboxamide (**16aa**), was filtered through a silica plug using EtOAc and was used at the cyclization step as is without additional purification. An oven-dried 1 mL Wheaton vial was charged with powdered KOH (7.6 mg, 0.136 mmol, 2.0 equiv) and anhydrous THF (400 μL). Crude amide 16aa (20 mg, 0.068 mmol) was added as a solution in anhydrous THF (400 μL). The mixture was vigorously stirred at 30 °C for 18 h, and then the reaction mixture was filtered through short plug of Silica gel eluting with EtOAc. The eluate was concentrated in vacuum. The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless oil (R_f = 0.25).

Yield 17.6 mg (0.060 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.26 (m, 7H), 7.25−7.21 (m, 1H), 7.10−7.08 (m, 2H), 4.71 (q, J = 14.7 Hz, 2H), 3.92 (ddd, J = 15.5, 12.6, 5.1 Hz, 1H), 3.53 (dd, J = 11.2, 5.1 Hz, 1H), 3.43 (dd, J = 6.3, 3.7 Hz, 1H), 3.41−3.36 (m, 1H), 3.03 (dt, J = 23.2, 11.6 Hz, 1H), 1.75 (dt, J = 24.0, 12.0 Hz, 1H), 1.49 (dd, J = 6.9, 6.4 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.7, 138.0, 137.3, 128.9 (+, 2C), 128.8 (+, 2C), 128.4 (+, 2C), 127.8 (+), 126.8 (+), 124.7 (+, 2C), 64.4 (−), 59.0 (+), 49.8 (−), 44.9 (−), 34.9, 22.5 (−). FTIR (NaCl, cm^{-1}): 1651, 1408, 1209, 1057. HRMS (TOF ES): found 294.1501, calculated for $C_{19}H_{20}NO_2$ (M + H) 294.1494 (2.4 ppm).

5-Methyl-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (17ab).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and 2-(methylamino)ethan-1-ol (**15b**) (141 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug, crude *N*-(2-hydroxyethyl)-*N*-methyl-1-phenylcycloprop-2-ene-1-carboxamide (**16ab**) was used at the cyclization step as is without additional purification. To this end, amide **16ab** (20 mg, 0.092 mmol) was treated with powdered KOH (10.3 mg, 0.184 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (1:1) as a colorless glass (R_f = 0.21). Yield 17.6 mg (0.081 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.27 (m, 2H), 7.25−7.19 (m, 1H), 7.05 (d, J = 7.9 Hz, 2H), 4.06 (ddd, J = 15.4, 12.7, 5.0 Hz, 1H), 3.82 (td, J = 11.9, 4.6 Hz, 1H), 3.64 (dd, J = 11.2, 5.0 Hz, 1H), 3.40 (dd, J = 6.2, 3.6 Hz, 1H), 3.08 (s, 3H), 3.03 (dd, J = 15.4, 4.7 Hz, 1H), 1.66 (dd, J = 6.9, 3.5 Hz, 1H), 1.45 (t, J = 6.6 Hz, 1H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.6, 137.9, 128.9 (+, 2C), 126.8 (+), 124.7 (+, 2C), 63.3 (−), 58.8 (+), 47.6 (−), 34.9, 34.3 (+), 22.3 (−). FTIR (NaCl, cm^{-1}): 1651, 1495, 1260, 1169. HRMS (TOF ES): found 240.1003, calculated for $C_{13}H_{15}NO_2Na$ (M + Na) 240.1000 (1.2 ppm).

5-(4-Methoxybenzyl)-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (17ac).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and 2-((4-methoxybenzyl)amino)ethan-1-ol (**15c**) (339 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-(2-hydroxyethyl)-*N*-(4-methoxybenzyl)-1-phenylcycloprop-2-ene-1-carboxamide (**16ac**) was used at the cyclization step as is without additional purification. To this end, amide 16ac (20 mg, 0.062 mmol) was treated with powdered KOH (6.9 mg, 0.124 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.21, mp 102−104 °C). Yield 18.2 mg (0.056 mmol, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.28 (m, 2H), 7.26−7.20 (m, 3H), 7.09−7.06 (m, 2H), 6.88−6.84 (m, 2H), 4.73 (d, J = 14.5 Hz, 1H), 4.57 (t, J = 11.7 Hz, 1H), 3.92−3.84 (m, 1H), 3.80 (s, J = 2.5 Hz, 3H), 3.51 (dd, J = 11.1, 5.1 Hz, 1H), 3.40 (dt, J = 11.1, 5.6 Hz, 1H), 3.34 (ddd, J = 12.5, 11.2, 4.9 Hz, 1H), 3.03 (dd, J = 15.4, 4.8 Hz, 1H), 1.74 (dd, J = 7.0, 3.6 Hz, 1H), 1.52−1.45 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.5, 159.3, 138.0, 129.7 (+, 2C), 129.4 (+), 128.9 (+, 2C), 126.7 (+), 124.7 (+, 2C), 114.2 (+, 2C), 64.5 (−), 59.0 (+), 55.4 (+), 49.2 (−), 44.7 (−), 35.0, 22.5 (−). FTIR (NaCl, cm^{-1}): 1647, 1512, 1248, 1177, 1032. HRMS (TOF ES): found 346.1412, calculated for $C_{20}H_{21}NO_3Na$ (M + Na) 346.1419 (2.0 ppm).

5-(2-Chlorobenzyl)-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (17ad).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (1**4a**) (200 mg, 1.25 mmol, 1.0 equiv) and 2-((2-chlorobenzyl)amino)ethan-1-ol (**15d**) (348 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-(2-chlorobenzyl)-*N*-(2-hydroxyethyl)-1-phenylcycloprop-2-ene-1-carboxamide (**16ad**) was isolated and used at the cyclization step without additional purification. To this end, amide **16ad** (20 mg, 0.061 mmol) was treated with powdered KOH (6.8 mg, 0.122 mmol). The titled product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless oil (R_f = 0.31). Yield 18.4 mg (0.056 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (dd, J = 7.2, 2.1 Hz, 1H), 7.37 (dd, J = 7.3, 1.9 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.28−7.18 (m, 3H), 7.14−7.07 (m, 2H), 4.94 (d, J = 15.4 Hz, 1H), 4.77 (d, J = 15.4 Hz, 1H), 3.99 (ddd, J = 15.5, 12.3, 5.4 Hz, 1H), 3.63−3.49 (m, 2H), 3.47 (dd, J = 6.2, 3.6 Hz, 1H), 3.10 (dd, J = 15.4, 4.5 Hz, 1H), 1.75 (dd, J = 7.0, 3.6 Hz, 1H), 1.48 (t, J = 6.6 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.9, 137.9, 134.9, 133.6, 130.0 (+), 129.7 (+), 129.0 (+), 129.0 (+, 2C), 127.4, 126.8, 124.8 (+, 2C), 64.4 (−), 58.8 (+), 47.1 (−), 45.4 (−), 34.9, 22.6 (−). FTIR (NaCl, cm^{-1}): 1655, 1464, 1431, 1202, 1153. HRMS (TOF ES): found 328.1112, calculated for $C_{19}H_{19}ClNO_2$ (M + H) 328.1104 (2.4 ppm).

5-(5-Bromo-2-fluorobenzyl)-7-phenyl-2-oxa-5-azabicyclo[5.1.0]-octan-6-one (17ae).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (14a) (250 mg, 1.56 mmol, 1.0 equiv) and 2-((5-bromo-2-fluorobenzyl)amino)ethan-1-ol (**15e**) (581 mg, 2.34 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-(5-bromo-2-fluorobenzyl)-*N*-(2-hydroxyethyl)-1-phenylcycloprop-2-ene-1-carboxamide (**16ae**) was isolated and used at the cyclization step without additional purification. To this end, amide **16ae** (20 mg, 0.051 mmol) was treated with powdered KOH (5.7 mg, 0.102 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless oil (R_f = 0.31). Yield 17.4 mg (0.045 mmol, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (dd, J = 6.6, 2.5 Hz, 1H), 7.40−7.35 (m, 1H), 7.35−7.29 (m, 2H), 7.26−7.20 (m, 1H), 7.07 (dd, J = 5.2, 3.3 Hz, 2H), 6.95 (t, J = 9.1 Hz, 1H), 4.87 (d, J = 15.2 Hz, 1H), 4.54 (d, J = 15.2 Hz, 1H), 4.00 (ddd, J = 15.6, 11.4, 6.3 Hz, 1H), 3.66−3.54 (m, 2H), 3.46 (dd, J = 6.2, 3.6 Hz, 1H), 3.13−3.03 (m, 1H), 1.74 (dd, J = 7.0, 3.6 Hz, 1H), 1.48 (t, J = 6.6 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.9, 160.1 (d, J = 246.4 Hz), 137.7, 133.4 (d, J = 4.2 Hz, +), 132.4 (d, J = 8.2 Hz, +), 129.0 (+, 2C), 126.9 (+), 126.7 (d, J = 16.3 Hz), 124.7 (+, 2C), 117.3 (d, J = 23.5 Hz, +), 117.1 (d, J = 3.4 Hz), 64.2 (−), 58.8 (+), 45.7 (−),43.2 (d, J = 3.7 Hz, −), 34.8, 22.6 (−). FTIR (NaCl, cm^{-1}): 1643, 1478, 1252, 1113. HRMS (TOF ES): found 412.0320, calculated for $C_{19}H_{17}BrFNO_2Na$ (M + Na) 412.0324 (1.0 ppm).

5,7-Diphenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (17af).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and 2-(phenylamino)ethan-1-ol (**15f**) (257 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a Silica gel plug crude *N*-(2-hydroxyethyl)-*N*,1-diphenylcycloprop-2-ene-1-carboxamide (**16af**) was isolated and used at the cyclization step without additional purification. To this end, amide **16af** (20 mg, 0.072

mmol) was treated with powdered KOH (8 mg, 0.144 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (1:1) as a colorless glass (R_f = 0.48). Yield 5.8 mg (0.021 mmol, 29%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44−7.39 (m, 2H), 7.38−7.31 (m, 4H), 7.30−7.25 (m, 2H), 7.19−7.16 (m, 2H), 4.37 (ddd, J = 15.4, 12.6, 4.9 Hz, 1H), 3.94 (ddd, J = 12.5, 11.5, 4.8 Hz, 1H), 3.76 (dd, J = 11.4, 4.9 Hz, 1H), 3.54 (dd, J = 6.3, 3.6 Hz, 1H), 3.47 (dd, J = 15.4, 4.7 Hz, 1H), 1.83 (dd, J = 7.1, 3.6 Hz, 1H), 1.55 (dd, J = 7.0, 6.3 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.4, 142.3, 137.8, 129.4 (+, 2C), 129.0 (+, 2C), 127.1 (+), 126.9 (+), 126.4 (+, 2C), 124.7 (+, 2C), 64.9 (−), 59.3 (+), 49.1 (−), 35.4, 22.6 (−). FTIR (NaCl, cm^{-1}): 1663, 1493, 1398, 1215, 1157. HRMS (TOF ES): found 280.1336, calculated for $C_{18}H_{18}NO_2$ (M + H) 280.1338 (0.7ppm).

5-(4-Methoxyphenyl)-7-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (17ag).— This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and 2-((4-methoxyphenyl)-amino)ethan-1-ol (15g) (313 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-(2-hydroxyethyl)-*N*-(4-methoxyphenyl)-1-phenylcycloprop-2-ene-1-carboxamide (**16ag**) was used at the cyclization step as is without additional purification. To this end, amide 16ag (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (1:1) as a colorless glass (R_f = 0.26). Yield 17 mg (0.055 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (t, J = 7.6 Hz, 2H), 7.29−7.20 (m, 3H), 7.16 (d, J = 7.6 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.34 (ddd, J = 15.4, 12.6, 4.9 Hz, 1H), 3.92 (td, J = 12.0, 4.7 Hz, 1H), 3.81 (s, 3H), 3.73 (dd, J = 11.3, 4.9 Hz, 1H), 3.52 (dd, J = 6.2, 3.6 Hz, 1H), 3.38 (dd, J = 15.3, 4.7 Hz, 1H), 1.81 (dt, J = 20.0, 10.0 Hz, 1H), 1.53 (t, J = 6.7 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.6, 158.4, 137.9, 135.2, 129.0 (+, 2C), 127.7 (+, 2C), 126.8 (+), 124.6 (+, 2C), 114.7 (+, 2C), 64.6 (−), 59.3 (+), 55.6 (+), 49.4 (−), 35.3, 22.6 (−). FTIR (NaCl, cm^{-1}): 1661, 1510, 1250, 1157. HRMS (TOF ES): found 332.1275, calculated for $C_{19}H_{19}NO_3Na$ (M + Na) 332.1263 (3.6 ppm).

6-Benzyl-8-phenyl-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (17ah).— This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and 3-(benzylamino)propan-1-ol (**15h**) (309 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-benzyl-*N*-(3-hydroxypropyl)-1-phenylcycloprop-2-ene-1-carboxamide (**16ah**) was used at the cyclization step as is without additional purification. To this end, amide **16ah** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexanes/EtOAc mixture (2:1) as a colorless solid (R_f = 0.31, mp 148−150 °C). Yield 18 mg (0.059 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29−7.17 (m, 7H), 7.15−7.11 (m, 1H), 7.04−7.00 (m, 2H), 5.33 (dd, J = 14.7, 1.2 Hz, 1H), 4.16 (dd, J = 12.7, 5.7 Hz, 1H), 3.97 (d, J = 14.7 Hz, 1H), 3.87−3.76 (m, 2H), 3.67 (td, J = 12.8, 3.4 Hz, 1H), 3.08 (dd, J = 15.5, 6.7 Hz, 1H), 2.04−1.92 (m, 1H), 1.79 (dd, J = 7.0, 4.5 Hz, 1H), 1.46 (ddd, J = 15.1, 6.7, 3.3 Hz, 1H), 1.27 (t, J = 7.2 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.5, 139.4, 137.7, 128.9 (+, 2C), 128.7 (+, 2C), 128.6 (+, 2C), 127.6 (+), 126.6 (+), 124.8 (+, 2C), 73.4 (−), 68.8 (+), 48.9 (−), 45.7 (−), 35.9,

29.3 (−), 22.5 (−). FTIR (NaCl, cm^{-1}): 1640, 1439, 1221, 1123. HRMS (TOF ES): found 330.1471, calculated for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470 (0.3 ppm).

5-Benzyl-7-(4-fluorophenyl)-2-oxa-5-azabicyclo[5.1.0]octan-6-one (17ba).—This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and 2-(benzylamino)ethan-1-ol (**15a**) (255 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-benzyl-1-(4-fluorophenyl)-*N*-(2-hydroxyethyl)cycloprop-2-ene-1-carboxamide (**16ba**) was used at the cyclization step as is without additional purification. To this end, amide **16ba** (20 mg, 0.064 mmol) was treated with powdered KOH (7.2 mg, 0.128 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (1:1) as a colorless glass (R_f =0.44). Yield 18 mg (0.058 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.27 (m, 5H), 7.12−7.04 (m, 2H), 7.00 (t, J = 8.6 Hz, 2H), 4.75−4.63 (m, 2H), 3.96−3.85 (m, 1H), 3.54 (dd, J = 11.2, 5.1 Hz, 1H), 3.44−3.34 (m, 2H), 3.05 (dd, J = 15.4, 4.8 Hz, 1H), 1.73 (dd, J = 6.9, 3.4 Hz, 1H), 1.41 (t, J = 6.6 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.6, 161.8 (d, J = 245.8 Hz), 137.2, 133.7 (d, J = 3.2 Hz, +, 2C), 128.9 (+, 2C), 128.3 (+, 2C), 127.9 (+), 126.5 (d, J = 8.0 Hz, +, 2C), 115.9 (d, J = 21.4 Hz, 2C, +), 64.4 (−), 58.5 (+), 49.9 (−), 44.9 (−), 34.4, 22.5 (−). FTIR (NaCl, cm^{-1}): 1649, 1512, 1230, 1153. HRMS (TOF ES): found 334.1207, calculated for $C_{19}H_{18}FNO_2Na$ (M+ Na) 334.1219 (3.6 ppm).

7-(4-Fluorophenyl)-5-methyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (17bb).—This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (14b) (200 mg, 1.12 mmol, 1.0 equiv) and 2-(methylamino)ethan-1-ol (15b) (126 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude 1-(4-fluorophenyl)-*N*-(2-hydroxyethyl)-*N*-methylcycloprop-2-ene-1-carboxamide (**16bb**) was used at the cyclization step as is without additional purification. To this end, amide **16bb** (20 mg, 0.085 mmol) was treated with powdered KOH (9.5 mg, 0.17 mmol). The product was isolated by column chromatography eluting with EtOAc as a colorless solid (R_f = 0.51, mp 104−105 °C). Yield 17.2 mg (0.073 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05−6.96 (m, 4H), 4.04 (ddd, J = 15.3, 12.7, 5.0 Hz, 1H), 3.86−3.76 (m, 1H), 3.69−3.61 (m, 1H), 3.38 (dd, J = 6.3, 3.5 Hz, 1H), 3.06 (s, 3H), 3.05−3.02 (m, 1H), 1.63 (dd, J = 7.0, 3.5 Hz, 1H), 1.38 (dd, J = 6.9, 6.4 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.5, 161.8 (d, J = 245.6 Hz), 133.6 (d, J = 3.1 Hz), 126.5 (d, J = 8.0 Hz, +, 2C), 115.8 (d, J = 21.4 Hz, +, 2C), 63.3 (−), 58.4 (+), 47.5 (−), 34.4, 34.3 (+), 22.3 (−). FTIR (NaCl, cm^{-1}): 1649, 1512, 1203, 1165. HRMS (TOF ES): found 236.1094, calculated for $C_{13}H_{15}FNO_2$ (M + H) 236.1087 (3.0 ppm).

7-(4-Fluorophenyl)-5-(4-methoxyphenyl)-2-oxa-5-azabicyclo-[5.1.0]octan-6-one (17bg).—This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and 2-((4-methoxyphenyl)amino)ethan-1-ol (**15g**) (282 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude 1-(4-fluorophenyl)-*N*-(2-hydroxyethyl)-*N*-(4-methoxyphenyl)cycloprop-2-ene (**16bg**) was used at the cyclization step as is without additional purification. To this end, amide **16bg** (20 mg, 0.061 mmol) was treated with

powdered KOH (6.9 mg, 0.122 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f 0.19, mp 132−133 °C). Yield 18.4 mg (0.056 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23− 7.18 (m, 2H), 7.17−7.12 (m, 2H), 7.07−7.01 (m, 2H), 6.95−6.90 (m, 2H), 4.32 (ddd, J = 15.4, 12.6, 4.9 Hz, 1H), 3.91 (td, J = 11.9, 4.7 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, J = 11.0, 5.1 Hz, 1H), 3.50 (dd, J = 6.2, 3.5 Hz, 1H), 3.38 (dt, J = 19.4, 9.7 Hz, 1H), 1.79 (dd, J = 7.1, 3.5 Hz, 1H), 1.45 (t, J = 6.7 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.5, 161.9 (d, J = 245.8 Hz), 158.5, 135.1, 133.6 (d, J = 3.1 Hz), 127.6 (+, 2C), 126.5 (d, J = 8.0 Hz, +, 2C), 115.9 (d, J = 21.5 Hz, +, 2C), 114.7 (+, 2C), 64.6 (−), 58.9 (+), 55.7 (+), 49.3 (−), 34.8, 22.6 (−). FTIR (NaCl, cm^{-1}): 1661, 1510, 1265, 1159. HRMS (TOF ES): found 350.1172, calculated for $C_{19}H_{18}FNO_3Na$ (M + Na) 350.1168 (1.1 ppm).

6-Benzyl-8-(4-fluorophenyl)-2-oxa-6-azabicyclo[6.1.0]nonan-7-one (17bh).— This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and 3-(benzylamino)propan-1-ol (**15h**) (278 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-benzyl-1-(4-fluorophenyl)-*N*-(3-hydroxypropyl)cycloprop-2-ene-1-carboxamide (**16bh**) was used at the cyclization step as is without additional purification. To this end, amide **16bh** (20 mg, 0.061 mmol) was treated with powdered KOH (6.9 mg, 0.122 mmol). The product was isolated by column chromatography, eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.19, mp 132−133 °C). Yield 17.6 mg (0.054 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.23 (m, 5H), 7.10−7.03 (m, 2H), 7.00−6.92 (m, 2H), 5.37 (d, J = 14.7 Hz, 1H), 4.22 (dd, J = 12.7, 5.6 Hz, 1H), 4.01 (d, J = 14.7 Hz, 1H), 3.90−3.80 (m, 2H), 3.73 (td, J = 12.7, 3.4 Hz, 1H), 3.14 (dd, J = 15.5, 6.7 Hz, 1H), 2.12−1.97 (m, 1H), 1.83 (dd, J = 7.0, 4.4 Hz, 1H), 1.54 (ddd, J = 15.2, 6.7, 3.2 Hz, 1H), 1.26 (dd, J = 9.6, 4.9 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.3, 161.6 (d, J = 245.7 Hz), 137.6, 135.1 (d, J = 3.1 Hz), 128.8 (+, 2C), 128.5 (+, 2C), 127.6 (+), 126.6 (d, J = 7.9 Hz, +, 2C), 115.8 (d, J = 21.5 Hz, +, 2C), 73.4 (−), 68.5 (+), 48.9 (−), 45.7 (−), 35.4, 29.3 (−), 22.4 (−). FTIR (NaCl, cm^{-1}): 1634, 1510, 1261, 1074. HRMS (TOF ES): found 348.1385, calculated for $C_{20}H_{20}FNO_2Na$ (M + Na) 348.1376 (2.6 ppm).

6-(2-Chlorobenzyl)-8-(4-fluorophenyl)-2-oxa-6-azabicyclo[6.1.0]-nonan-7-one (17bi).—This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and 3-((2-chlorobenzyl)amino)propan-1-ol (**15i**) (336 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-(2-chlorobenzyl)-1-(4-fluorophenyl)-*N*-(3-hydroxypropyl)cycloprop-2-ene-1-carboxamide (**16bi**) was used at the cyclization step as is without additional purification. To this end, amide **16bi** (20 mg, 0.056 mmol) was treated with powdered KOH (6.2 mg, 0.112 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless glass (R_f = 0.19). Yield 18.4 mg (0.051 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.33 (m, 1H), 7.30−7.25 (m, 1H), 7.23−7.17 (m, 2H), 7.15−7.09 (m, 2H), 7.02−6.94 (m, 2H), 5.29 (d, J = 15.4 Hz, 1H), 4.36 (d, J = 15.4 Hz, 1H), 4.24 (dd, J = 12.8, 5.6 Hz, 1H), 3.94 (dd, J = 15.6, 11.2 Hz, 1H), 3.90 (dd, J = 7.5, 4.4 Hz, 1H), 3.75 (tt, J = 14.4, 7.2 Hz, 1H), 3.15 (dd, J =

15.5, 6.6 Hz, 1H), 2.17−2.04 (m, 1H), 1.82 (dd, *J* = 7.0, 4.4 Hz, 1H), 1.58 (ddd, *J* = 15.1, 6.5, 3.1 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): *δ* 170.6, 161.7f (d, *J* = 245.7 Hz), 135.0, 134.9 (d, *J* = 3.2 Hz), 133.8, 129.9 (+), 129.6 (+), 128.8 (+), 127.2 (+), 126.9 (d, *J* = 7.8 Hz, +, 2C), 115.8 (d, *J* = 21.6 Hz, +, 2C), 73.4 (−), 68.1 (+), 46.3 (−), 46.3 (−), 35.4, 29.5 (−), 22.4 (−). FTIR (NaCl, cm^{-1}): 1638, 1510, 1223, 1165. HRMS (TOF ES): found 382.1001, calculated for $C_{20}H_{19}ClFNO_2Na$ (M + Na) 382.0986 (3.9 ppm).

5-Benzyl-7-(2,4-dichlorophenyl)-2-oxa-5-azabicyclo[5.1.0]octan-6-one (17ca).— This compound was synthesized according to the typical procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**14c**) (200 mg, 0.87 mmol, 1.0 equiv) and 2-(benzylamino)ethan-1-ol (**15a**) (198 mg, 1.31 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-benzyl-1-(2,4-dichlorophenyl)-*N*-(2-hydroxyethyl)cycloprop-2-ene-1-carboxamide (**16ca**) was used at the cyclization step as is without additional purification. To this end, amide **16ca** (20 mg, 0.055 mmol) was treated with powdered KOH (6.2 mg, 0.11 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless oil (R_f = 0.29). Yield 16 mg (0.044 mmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.70 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 2.2 Hz, 1H), 7.31−7.19 (m, 6H), 4.81 (d, *J* = 14.8 Hz, 1H), 4.63 (ddd, *J* = 15.6, 12.4, 5.4 Hz, 1H), 4.37 (d, *J* = 14.8 Hz, 1H), 4.01 (dd, *J* = 6.3, 3.2 Hz, 1H), 3.71 (dd, *J* = 11.3, 5.3 Hz, 1H), 3.42−3.30 (m, 1H), 3.06 (dd, *J* = 15.5, 5.2 Hz, 1H), 1.72 (dd, *J* = 6.6, 3.2 Hz, 1H), 1.34 (t, *J* = 6.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): *δ* 170.2, 137.2, 134.7, 134.0, 133.9, 133.8 (+), 130.7 (+), 128.8 (+, 2C), 128.2 (+, 2C), 127.8 (+), 127.6 (+), 64.5 (−), 56.5 (+), 50.7 (−), 44.5 (−), 34.2, 22.4 (−). FTIR (NaCl, cm^{-1}): 1647, 1472, 1076. HRMS (TOF ES): found 384.0522, calculated for $C_{19}H_{17}Cl_2NO_2Na$ (M + Na) 384.0534 (3.1 ppm).

7-(2,4-Dichlorophenyl)-5-methyl-2-oxa-5-azabicyclo[5.1.0]-octan-6-one (17cb).— This compound was synthesized according to the typical procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**14c**) (200 mg, 0.87 mmol, 1.0 equiv) and 2-(methylamino)ethan-1-ol (15b) (98 mg, 1.31 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude 1-(2,4-dichlorophenyl)-*N*-(2-hydroxyethyl)-*N*-methylcycloprop-2-ene-1-carboxamide (**16cb**) was used at the cyclization step as is without additional purification. To this end, amide **16cb** (20 mg, 0.07 mmol) was treated with powdered KOH (7.8 mg, 0.14 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (1:2) as a colorless solid (R_f = 0.30, mp 139−140 °C). Yield 15.8 mg (0.055 mmol, 79%). ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.66 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 2.2 Hz, 1H), 7.21 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.82−4.69 (m, 1H), 4.01 (dd, *J* = 6.3, 3.2 Hz, 1H), 3.87−3.80 (m, 2H), 3.05 (ddd, *J* = 8.1, 5.9, 3.6 Hz, 1H), 2.97 (s, 3H), 1.62 (dd, *J* = 6.5, 3.2 Hz, 1H), 1.28 (t, *J* = 6.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): *δ* 170.0, 134.4, 134.0, 133.8, 133.7 (+), 130.7 (+), 127.5 (+), 63.4 (−), 56.2 (+), 46.9 (−), 35.1 (+), 34.1, 22.3 (−). FTIR (NaCl, cm^{-1}): 1647, 1474, 1253, 1169. HRMS (TOF ES): found 308.0210, calculated for $C_{13}H_{13}Cl_2NO_2Na$ (M + Na) 308.0221 (3.6 ppm).

6-Benzyl-8-(2,4-dichlorophenyl)-2-oxa-6-azabicyclo[6.1.0]-nonan-7-one (17ch).— This compound was synthesized according to the typical procedure from 1-(2,4-

dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**14c**) (200 mg, 0.87 mmol, 1.0 equiv) and 3-(benzylamino)propan-1-ol (**15h**) (216 mg, 1.31 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-benzyl-1-(2,4-dichlorophenyl)-*N*-(3-hydroxypropyl)cycloprop-2-ene-1-carboxamide (**16ch**) was used at the cyclization step as is without additional purification. To this end, amide **16ch** (20 mg, 0.053 mmol) was treated with powdered KOH (6 mg, 0.106 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (1:1) as a colorless solid (R_f = 0.37, mp 151−153 °C). Yield 17 mg (0.045 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.26−7.18 (m, 4H), 7.13− 7.03 (m, 2H), 5.23 (d, J = 15.0 Hz, 1H), 4.45−4.35 (m, 2H), 4.19 (dt, J = 25.4, 12.7 Hz, 1H), 4.05−3.92 (m, 2H), 3.07 (dd, J = 15.5, 6.6 Hz, 1H), 2.06−1.95 (m, 1H), 1.94 (dd, J = 6.7, 4.3 Hz, 1H), 1.94 (dd, J = 6.7, 4.3 Hz, 1H), 1.16−1.13 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 169.9, 137.5, 134.7, 134.6, 133.9, 133.5 (+), 130.8 (+), 128.7 (+, 2C), 128.0 (+, 2C), 127.6 (+), 127.4 (+), 72.6 (−), 66.2 (+), 49.6 (−), 45.5 (−), 35.7, 29.8 (−), 21.6 (−). FTIR (NaCl, cm^{-1}): 1643, 1473, 1219, 1105. HRMS (TOF ES): found 398.0709, calculated for $C_{20}H_{19}Cl_2NO_2Na$ (M + Na) 398.0691 (4.5 ppm).

(+)-(1S,4S,7S)-4-Benzyl-5-methyl-7-phenyl-2-oxa-5-azabicyclo-[5.1.0]octan-6-one (19aa).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and (*S*)-2-(methylamino)-3-phenylpropan-1-ol (**30a**) (309 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude (*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-*N*-methyl-1-phenylcycloprop-2-ene-1-carboxamide (**18aa**) was used at the cyclization step as is without additional purification. To this end, amide **18aa** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (1:1) as a colorless oil (R_f = 0.38). Yield 18.2 mg (0.059 mmol, 91%). $[\alpha]_D^{20}$ +45.3 (c = 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.23 (m, 6H), 7.03−6.97 (m, 4H), 4.66 (dddd, J = 10.8, 9.6, 5.9, 4.9 Hz, 1H), 3.66−3.52 (m, 2H), 3.42 (dd, J = 6.2, 3.5 Hz, 1H), 2.93 (s, 3H), 2.91 (dd, J = 15.0, 9.6 Hz, 1H), 2.80 (dd, J = 14.9, 5.8 Hz, 1H), 1.71 (dd, J = 7.1, 3.6 Hz, 1H), 1.52 (dd, J = 7.1, 6.3 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.8, 137.7, 136.7, 128.8 (+, 2C), 128.8 (+, 2C), 128.6 (+, 2C), 127.0 (+), 126.9 (+), 124.7 (+, 2C), 67.6 (−), 59.8 (+), 54.8 (+), 35.1, 34.1 (−), 27.3 (+), 23.0 (−). FTIR (NaCl, cm^{-1}): 1649, 1497, 1200. HRMS (TOF ES): found 330.1480, calculated for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470 (3.0 ppm).

(+)-(1S,4S,7S)-4,5-Dibenzyl-7-phenyl-2-oxa-5-azabicyclo[5.1.0]-octan-6-one (19ab).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and (*S*)-2-(benzylamino)-3-phenylpropan-1-ol (**30b**) (452 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-*N*-(1-hydroxy-3-phenylpropan-2-yl)-1-phenylcycloprop-2-ene-1-carboxamide (**18ab**) was used at the cyclization step as is without additional purification. To this end, amide **18ab** (20 mg, 0.052 mmol) was treated with powdered KOH (5.8 mg, 0.104 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless glass (R_f = 0.31). Yield 18.6 mg (0.048 mmol, 93%). $[\alpha]_D^{20}$ +67.0 (c = 1.1, $CHCl_3$). ^{1}H NMR (500 MHz,

$CDCl_3$): δ 7.39−7.22 (m, 11H), 7.13−7.09 (m, 2H), 7.03−6.98 (m, 2H), 5.44 (d, J = 15.8 Hz, 1H), 4.76 (dddd, J = 11.7, 9.1, 6.1, 4.5 Hz, 1H), 4.06 (d, J = 15.7 Hz, 1H), 3.50 (dd, J = 6.3, 3.6 Hz, 1H), 3.44 (dd, J = 11.1, 4.5 Hz, 1H), 3.07 (t, J = 11.4 Hz, 1H), 2.98 (dd, J = 15.2, 9.2 Hz, 1H), 2.69 (dd, J = 15.2, 6.1 Hz, 1H), 1.90 (dd, J = 7.1, 3.5 Hz, 1H), 1.58 (dd, J = 7.1, 6.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 172.0, 138.9, 137.7, 136.9, 128.9 (+, 2C), 128.9 (+, 2C), 128.7 (+, 2C), 128.3 (+, 2C), 127.5 (+, 2C), 127.4 (+), 127.0 (+), 127.0 (+), 124.9 (+, 2C), 69.5 (−), 59.9 (+), 54.8 (+), 44.8 (−), 35.2, 33.5 (−), 23.3 (−). FTIR (NaCl, cm^{-1}): 1649, 1497, 1207, 1055. HRMS (TOF ES): found 406.1770, calculated for $C_{26}H_{25}NO_2Na$ (M + Na) 406.1783 (3.2 ppm).

(+)-(1S,4S,7S)-5-Benzyl-4-isobutyl-7-phenyl-2-oxa-5-azabicyclo-[5.1.0]octan-6-one (19ad).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and (*S*)-2-(benzylamino)-4-methylpentan-1-ol (**30d**) (388 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-*N*-(1-hydroxy-4-methylpentan-2-yl)-1-phenylcycloprop-2-ene-1-carboxamide (**18ad**) was used at the cyclization step as is without additional purification. To this end, amide **18ad** (20 mg, 0.057 mmol) was treated with powdered KOH (6.4 mg, 0.114 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.38, mp 117−118 °C). Yield 18.8 mg (0.054 mmol, 94%). $[\alpha]_D^{20}$ +83.4 (c = 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.35−7.20 (m, 8H), 7.12−7.07 (m, 2H), 5.39 (d, J = 15.7 Hz, 1H), 4.37−4.25 (m, 1H), 4.12 (d, J = 15.5 Hz, 1H), 3.46 (dd, J = 6.2, 3.6 Hz, 1H), 3.35 (dd, J = 11.1, 4.5 Hz, 1H), 2.99− 2.87 (m, 1H), 1.86 (dd, J = 7.1, 3.5 Hz, 1H), 1.65 (ddd, J = 14.2, 9.7, 4.4 Hz, 1H), 1.57 (dd, J = 7.1, 6.3 Hz, 1H), 1.55−1.46 (m, 1H), 0.98 (ddd, J = 14.3, 9.0, 4.4 Hz, 1H), 0.82 (d, J = 6.7 Hz, 3H), 0.63 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 172.4, 138.9, 137.9, 128.9 (+, 2C), 128.6 (+, 2C), 127.7 (+, 2C), 127.3 (+), 126.8 (+), 124.6 (+, 2C), 69.6 (−), 60.0 (+), 52.9 (+), 44.7 (−), 36.3 (−), 35.2, 25.3 (+), 23.2 (−), 23.1 (+), 21.7 (+). FTIR (NaCl, cm^{-1}): 1647, 1497, 1219, 1029. HRMS (TOF ES): found 372.1926, calculated for $C_{23}H_{27}NO_2Na$ (M + Na) 372.1939 (3.5 ppm).

(+)-(1S,4S,7S)-4-Benzyl-7-(4-fluorophenyl)-5-methyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (19ba).—This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)-cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and (*S*)-2-(methylamino)-3-phenylpropan-1-ol (30a) (278 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude (*S*)-1-(4-fluorophenyl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-*N*-methylcycloprop-2-ene-1-carboxamide (**18ba**) was used at the cyclization step as is without additional purification. To this end, amide **18ba** (20 mg, 0.061 mmol) was treated with powdered KOH (6.8 mg, 0.122 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless oil (R_f = 0.1). Yield 19.2 mg (0.059 mmol, 96%). $[\alpha]_D^{20}$ +41.0 (c = 0.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.28−7.22 (m, 3H), 7.04−6.92 (m, 6H), 4.70−4.53 (m, 1H), 3.68−3.51 (m, 2H), 3.39 (dd, J = 6.3, 3.5 Hz, 1H), 2.98−2.89 (m,1H), 2.92 (s, 3H), 2.80 (dd, J = 14.9, 5.8 Hz, 1H), 1.69 (dd, J = 7.2, 3.5 Hz, 1H), 1.45 (dd, J = 7.2, 6.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.5, 161.9 (d, J = 245.6 Hz), 136.7, 133.4 (d, J = 3.1 Hz), 128.8 (+, 2C), 128.5 (+, 2C), 127.1 (+), 126.4 (d, J = 7.9 Hz, +, 2C),

115.7 (d, J = 21.4 Hz, +, 2C), 67.5 (−), 59.5 (+), 55.1 (+), 34.6, 34.1 (−), 27.3 (+), 23.0 (−). FTIR (NaCl, cm^{-1}): 1647, 1510, 1049. HRMS (TOF ES): found 348.1390, calculated for $C_{20}H_{20}FNO_2Na$ (M + Na) 348.1376 (4.0 ppm).

(+)-(1S,4S,7S)-4,5-Dibenzyl-7-(4-fluorophenyl)-2-oxa-5-azabicyclo[5.1.0]octan-6-one (19bb).—This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)-cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and (*S*)-2-(benzylamino)-3-phenylpropan-1-ol (**30b**) (406 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude (*S*)-N-benzyl-1-(4-fluorophenyl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)cycloprop-2-ene-1-carboxamide (**18bb**) was used at the cyclization step as is without additional purification. To this end, amide **18bb** (20 mg, 0.05 mmol) was treated with powdered KOH (5.6 mg, 0.1 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless glass (R_f = 0.31). Yield 18 mg (0.045 mmol, 90%). $[\alpha]_D^{20}$ +53.0 (c = 0.90, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.30 (m, 4H), 7.28−7.22 (m, 4H), 7.11−7.02 (m, 4H), 6.99 (dd, J = 7.4, 2.1 Hz, 2H), 5.41 (d, J = 15.7 Hz, 1H), 4.71 (dddd, J = 11.8, 9.0, 6.2, 4.5 Hz, 1H), 4.06 (d, J = 15.7 Hz, 1H), 3.48 (dd, J = 6.4, 3.6 Hz, 1H), 3.44 (dd, J = 11.2, 4.6 Hz, 1H), 3.07 (t, J = 11.4 Hz, 1H), 2.99 (dd, J = 15.1, 9.0 Hz, 1H), 2.69 (dd, J = 15.1, 6.2 Hz, 1H), 1.87 (dd, J = 7.2, 3.5 Hz, 1H), 1.50 (dd, J = 7.1, 6.3 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.9, 161.9 (d, J = 245.8 Hz), 138.8, 136.9, 133.5 (d, J = 3.2 Hz), 129.0 (+, 2C), 128.7 (+, 2C), 128.3 (+, 2C), 127.5 (+), 127.4 (+, 2C), 127.1 (+), 126.6 (d, J = 7.9 Hz, +, 2C), 115.8 (d, J = 21.7 Hz, +, 2C), 69.5 (−), 59.5 (+), 55.0 (+), 44.9 (−), 34.7, 33.6 (−), 23.3 (−). FTIR (NaCl, cm^{-1}): 1649, 1512, 1233, 1165. HRMS (TOF ES): found 424.1707, calculated for $C_{26}H_{24}FNO_2Na$ (M + Na) 424.1689 (4.2 ppm).

(−)-(1R,4R,7R)-5-Benzyl-7-(4-fluorophenyl)-4-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (19bc).—This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)-cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and (*R*)-2-(benzylamino)-2-phenylethan-1-ol (**30c**) (383 mg, 1.68 mmol, 1.5 equiv). After extraction the (*R*)-*N*-benzyl-1-(4-fluorophenyl)-*N*-(2-hydroxy-1-phenylethyl)cycloprop-2-ene-1-carbox-amide (**18bc**) was isolated by column chromatography eluting with a dichloromethane/EtOAc mixture (3:1) as a mixture of rotamers in a ratio of 2.2:1 as a colorless solid (R_f = 0.33, mp 158−159 °C). Yield 146.7 mg (0.38 mmol, 34%). $[\alpha]_D^{20}$−28.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ [7.44−7.20 (m), Σ8H], [7.10−7.06 (m), 7.01−6.92 (m), 6.80 (br. m), Σ6H], [5.48−5.42 (m), 5.22 (dd, J = 8.4, 4.6 Hz), Σ1H], [5.11 (d, J = 15.1 Hz), 4.42 (d, J = 16.9 Hz), 4.20 (d, J = 16.9 Hz), 3.87 (d, J = 15.0 Hz), Σ2H], [4.15−4.08 (m), 4.06−4.00 (m), 3.81−3.65 (br. m), 3.63−3.55 (br. m), Σ2H], [1.72 (br.s), 1.40 (br. s), Σ1H]. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ Major rotamer: 176.9, 161.8 (d, J = 245.4 Hz), 138.4 (d, J = 2.7 Hz), 137.7, 137.0, 128.8 (+, 4C), 128.5 (+, 2C), 128.2 (+),127.8 (d, J = 7.8 Hz, +, 2C), 127. Six (+), 126.8 (+, 2C), 115.5 (d, J = 21.2 Hz, +, 2C), 110.2 (+), 109.8 (+), 63.9 (−), 63.1 (+), 50.6 (−), 32.6. Minor rotamer: 176.1, 161.9 (d, J = 246.1 Hz), 139.3, 139.0 (d, J = 2.6 Hz), 136.6, 128.9 (+, 4C), 128.1 (+), 127.8 (+, 2C), 127.5 (+), 128.4 (d, J = 7.9 Hz, +, 2C), 127.6 (+, 2C), 115.5 (d, J = 21.2 Hz, +, 2C), 111.7 (+), 110.4 (+), 62.5 (+), 62.4 (−), 45.7 (−), 29.8. FTIR (NaCl, cm^{-1}): 3366 (br), 1605, 1492, 1231, 1159. HRMS (TOF ES): found 410.1512, calculated for

$C_{25}H_{22}FNO_2Na$ (M + Na) 410.1532 (4.9 ppm). To this end, amide **18bc** (20 mg, 0.052 mmol) was treated with powdered KOH (5.8 mg, 0.104 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.4, mp 192−194 °C). Yield 17.8 mg (0.046 mmol, 89%). $[\alpha]_D^{20}$−82.6 (c = 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.37−7.31 (m, 1H), 7.32−7.26 (m, 2H), 7.19−7.16 (m, 5H), 7.12−7.06 (m, 2H), 6.96−6.89 (m, 4H), 5.46 (dd, *J* = 11.7, 5.1 Hz, 1H), 5.04 (d, *J* = 15.3 Hz, 1H), 3.82−3.71 (m, 3H), 3.52 (dd, *J* = 6.3, 3.5 Hz, 1H), 1.92 (dd, *J* = 7.2, 3.5 Hz, 1H), 1.59 (dd, *J* = 7.2, 6.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.1, 161.9 (d, *J* = 245.8 Hz), 138.3, 133.9 (d, *J* = 3.0 Hz), 132.6, 129.7 (+, 2C), 129.3 (+), 128.9 (+, 2C), 128.2 (+, 2C), 127.7 (+, 2C), 127.1 (+), 126.3 (d, *J* = 7.9 Hz, +, 2C), 116.1 (d, *J* = 21.5 Hz, +, 2C), 67.2 (−), 59.9 (+), 58.5 (+), 45.6 (−), 34.7, 23.2 (−). FTIR (NaCl, cm^{-1}): 1651, 1510, 1223, 1165. HRMS (TOF ES): found 410.1539, calculated for $C_{25}H_{22}FNO_2Na$ (M + Na) 410.1532 (1.7 ppm).

(+)-(1S,4S,7S)-5-Benzyl-7-(4-fluorophenyl)-4-isobutyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (19bd).—This compound was synthesized according to a typical procedure from 1-(4-fluorophenyl)-cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and (*S*)-2-(benzylamino)-4-methylpentan-1-ol (**30d**) (349 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-1-(4-fluorophenyl)-*N*-(1-hydroxy-4-methylpentan-2-yl) cycloprop-2-ene-1-carboxamide (**18bd**) was used at the cyclization step as is without additional purification. To this end, amide **18bd** (20 mg, 0.054 mmol) was treated with powdered KOH (6.1 mg, 0.108 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.35, mp 139−141 °C). Yield 18.6 mg (0.05 mmol, 93%). $[\alpha]_D^{20}$ +79.3 (c = 0.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.31−7.21 (m, 5H), 7.12−7.06 (m, 2H), 7.05−6.99 (m, 2H), 5.37 (d, *J* = 15.5 Hz, 1H), 4.29 (ddt, *J* = 11.9, 9.2, 4.5 Hz, 1H), 4.10 (d, *J* = 15.5 Hz, 1H), 3.45 (dd, *J* = 6.3, 3.5 Hz, 1H), 3.36 (dd, *J* = 11.0, 4.5 Hz, 1H), 2.99−2.89 (m, 1H), 1.84 (dd, *J* = 7.1, 3.5 Hz, 1H), 1.65 (ddd, *J* = 14.2, 9.4, 4.6 Hz, 1H), 1.56−1.46 (m, 1H), 1.49 (dd, *J* = 7.1, 6.3 Hz, 1H), 1.00 (ddd, *J* = 14.4, 9.0, 4.5 Hz, 1H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.65 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 172.2, 161.8 (d, *J* = 245.6 Hz), 138.7, 133.7 (d, *J* = 3.2 Hz), 128.6 (+, 2C), 127.7 (+, 2C), 127.4 (+), 126.4 (d, *J* = 7.9 Hz, +, 2C), 115.8 (d, *J* = 21.5 Hz, +, 2C), 69.6 (−), 59.5 (+), 52.9 (+), 44.7 (−), 36.2 (−), 34.7, 25.3 (+), 23.3 (−), 23.0 (+), 21.8 (+). FTIR (NaCl, cm^{-1}): 1649, 1496, 1207, 1055. HRMS (TOF ES): found 368.2028, calculated for $C_{23}H_{27}FNO_2$ (M + H) 368.2026 (0.5 ppm).

(+)-(1S,4S,7S)-4-Benzyl-7-(2,4-dichlorophenyl)-5-methyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (19ca).—This compound was synthesized according to the typical procedure from 1-(2,4-dichlorophenyl)-cycloprop-2-ene-1-carboxylic acid (**14c**) (200 mg, 0.87 mmol, 1.0 equiv) and (*S*)-2-(methylamino)-3-phenylpropan-1-ol (**30a**) (216 mg, 1.31 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude (*S*)-1-(2,4-dichlorophenyl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-*N*-methylcycloprop-2-ene-1-carboxamide (**18ca**) was used at the cyclization step as is without additional purification. To this end, amide **18ca** (20 mg, 0.053 mmol) was treated with powdered KOH (5.9 mg, 0.106 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc

mixture (1:1) as a colorless oil (R_f = 0.5). Yield 16.8 mg (0.045 mmol, 84%). $[\alpha]_D^{20}$ +36.5 (c = 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.31−7.19 (m, 4H), 7.15−7.10 (m, 2H), 5.15 (ddt, J = 11.9, 7.7, 3.8 Hz, 1H), 4.07 (dd, J = 6.3, 3.2 Hz, 1H), 3.75 (dd, J = 11.4, 4.4 Hz, 1H), 3.54 (t, J = 11.3 Hz, 1H), 3.04 (dd, J = 14.3, 7.7 Hz, 1H), 2.88 (s, 3H), 2.83 (dd, J = 14.3, 7.7 Hz, 1H), 1.66 (dd, J = 6.7, 3.2 Hz, 1H), 1.39 (t, J = 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.0, 136.9, 133.9, 133.9, 133.7 (+), 133.5, 130.7 (+), 128.9 (+, 2C), 128.7 (+, 2C), 127.6 (+), 127.1 (+), 67.5 (−), 56.9 (+), 54.4 (+), 35.0 (−), 34.6, 28.2 (+), 22.9 (−). FTIR (NaCl, cm^{-1}): 1645, 1474, 1200, 1152. HRMS (TOF ES): found 398.0704, calculated for $C_{20}H_{19}Cl_2NO_2Na$ (M + Na) 398.0691 (3.3 ppm).

(+)-(1S,4S,7S)-4,5-Dibenzyl-7-(2,4-dichlorophenyl)-2-oxa-5-azabicyclo[5.1.0]octan-6-one (19cb).—This compound was synthesized according to the typical procedure from 1-(2,4-dichlorophenyl)-cycloprop-2-ene-1-carboxylic acid (**14c**) (200 mg, 0.87 mmol, 1.0 equiv) and (*S*)-2-(benzylamino)-3-phenylpropan-1-ol (**30b**) (316 mg, 1.31 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-1-(2,4-dichlorophenyl)-*N*-(1-hydroxy-3-phenylpropan-2-yl)cycloprop-2-ene-1-carboxamide (**18cb**) was used at the cyclization step as is without additional purification. To this end, amide **18cb** (20 mg, 0.044 mmol) was treated with powdered KOH (4.9 mg, 0.088 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless oil (R_f = 0.44). Yield 17.4 mg (0.038 mmol, 87%). $[\alpha]_D^{20}$ +56.6 (c = 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.34−7.19 (m, 9H), 7.13−7.07 (m, 2H), 5.26 (dt, J = 7.9, 4.0 Hz, 1H), 5.20 (d, J = 15.8 Hz, 1H), 4.16 (d, J = 15.7 Hz, 1H), 4.10 (dd, J = 6.3, 3.3 Hz, 1H), 3.64 (dd, J = 11.3, 4.5 Hz, 1H), 3.13 (t, J = 11.3 Hz, 1H), 3.08 (dd, J = 14.4, 7.3 Hz, 1H), 2.76 (dd, J = 14.4, 7.9 Hz, 1H), 1.82 (dd, J = 6.6, 3.2 Hz, 1H), 1.43 (t, J = 6.5 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.5, 138.7, 137.0, 134.1, 134.0 (+), 133.7, 130.7 (+), 129.0 (+, 2C), 128.7 (+, 2C), 128.5 (+, 2C), 127.7 (+), 127.4 (+, 2C), 127.4 (+), 127.1 (+), 69.2 (−), 57.3 (+), 54.4 (+), 45.6 (−), 34.6, 34.5 (−), 23.3 (−). FTIR (NaCl, cm^{-1}): 1647, 1473, 1244, 1030. HRMS (TOF ES): found 452.1195, calculated for $C_{26}H_{24}Cl_2NO_2$ (M + H) 452.1184 (2.4 ppm).

(+)-(1S,4S,7S)-5-Benzyl-7-(2,4-dichlorophenyl)-4-isobutyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (19cd).—This compound was synthesized according to the typical procedure from 1-(2,4-dichlorophenyl)-cycloprop-2-ene-1-carboxylic acid (**14c**) (200 mg, 0.87 mmol, 1.0 equiv) and (*S*)-2-(benzylamino)-4-methylpentan-1-ol (**30d**) (272 mg, 1.31 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude (*S*)-*N*-benzyl-1-(2,4-dichlorophenyl)-*N*-(1-hydroxy-4-methylpentan-2-yl)cycloprop-2-ene-1-carboxamide (**18cd**) was used at the cyclization step as is without additional purification. To this end, amide **18cd** (20 mg, 0.048 mmol) was treated with powdered KOH (5.4 mg, 0.096 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.53, mp 144−146 °C). Yield 18 mg (0.043 mmol, 90%). $[\alpha]_D^{20}$ +77.6 (c = 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.28−7.19 (m, 6H), 5.28 (d, J = 15.6 Hz, 1H), 4.87 (ddt, J = 11.7, 9.5, 4.8 Hz, 1H), 4.15 (dd, J = 6.3, 3.2 Hz, 1H), 4.02 (d, J = 15.6 Hz, 1H), 3.60 (dd, J = 11.2, 4.7 Hz, 1H), 2.97 (t, J = 11.4 Hz, 1H), 1.81 (dd, J = 6.7, 3.2 Hz, 1H), 1.66 (ddd, J =

14.1, 9.1, 5.0 Hz, 1H), 1.62−1.50 (m, 1H), 1.41 (t, J = 6.5 Hz, 1H), 1.12 (ddd, J = 13.8, 8.6, 5.0 Hz, 1H), 0.91 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.8, 138.7, 134.2, 133.9, 133.6, 133.6 (+), 130.8 (+), 128.6 (+, 2C), 127.5 (+, 3C), 127.3 (+), 69.6 (−), 57.2 (+), 52.1 (+), 45.2 (−), 36.7 (−), 34.4, 25.4 (+), 23.2 (−), 23.2 (+), 22.3 (+). FTIR (NaCl, cm^{-1}): 1647, 1473, 1217, 1005. HRMS (TOF ES): found 440.1143, calculated for $C_{23}H_{25}Cl_2NO_2Na$ (M + Na) 440.1160 (3.9 ppm).

(1S,3R,7S)- and (1R,3R,7R)-5-Benzyl-7-(4-fluorophenyl)-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (22b and 23b).—These compounds were synthesized according to the typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and (*R*)-2-(benzylamino)-1-phenylethan-1-ol (**31**) (383 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude (*R*)-*N*-benzyl-1-(4-fluorophenyl)-*N*-(2-hydroxy-2-phenylethyl)cycloprop-2-ene-1-carboxamide (**21b**) was used at the cyclization step as is without additional purification. To this end, amide **21b** (20 mg, 0.052 mmol) was treated with powdered KOH (5.8 mg, 0.104 mmol). The reaction mixture was vigorously stirred at 50 °C for 48 h. The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a mixture of diastereomers in a ratio of 4:1 as a colorless oil (R_f = 0.30). Yield 18.8 mg (0.049 mmol, 94%). ^1H NMR (500 MHz, $CDCl_3$): δ Major diastereomer: 7.43−7.19 (m, 10H), 7.12−7.03 (m, 2H), 7.03−6.95 (m, 2H), 4.79 (dd, J = 32.0, 14.8 Hz, 2H), 4.54 (dd, J = 11.6, 4.4 Hz, 1H), 4.10 (dd, J = 15.2, 11.5 Hz, 1H), 3.58 (dd, J = 6.3, 3.5 Hz, 1H), 3.47 (dd, J = 15.3, 4.5 Hz, 1H), 1.79 (dd, J = 6.9, 3.5 Hz, 1H), 1.42 (t, J = 6.6 Hz, 1H). Minor diastereomer: 7.43−7.19 (m, 10H), 7.12−7.03 (m, 2H), 7.03−6.95 (m, 1H), 6.92−6.90 (m, 1H), 5.37 (d, J = 14.8 Hz, 1H), 4.85 (d, J = 4.7 Hz, 1H), 4.15 (dd, J = 15.0, 4.6 Hz, 1H), 3.71 (dd, J = 6.2, 3.5 Hz, 1H), 3.16 (d, J = 15.3 Hz, 1H), 2.82 (d, J = 14.8 Hz, 1H), 1.95 (dd, J = 7.0, 3.4 Hz, 1H), 1.53 (dd, J = 7.1, 6.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ Major diastereomer: 170.6, 161.8 (d, J = 245.8 Hz), 137.5, 137.1, 133.5 (d, J = 3.2 Hz), 129.0 (+, 2C), 129.0 (+, 2C), 128.4 (+), 128.4 (+, 2C), 128.0 (+), 126.7 (d,z J = 8.1 Hz, +, 2C), 126.4 (+, 2C), 115.9 (d, J = 21.6 Hz, +, 2C), 74.3 (+), 55.1 (+), 50.2 (−), 48.5 (−), 34.5, 22.4 (−). Minor diastereomer: 170.5, 161.8 (d, J = 246.1 Hz), 140.0, 137.0, 133.7 (d, J = 3.2 Hz), 128.7 (+, 2C), 128.7 (+, 2C), 128.3 (+, 2C), 128.2 (+), 127.7 (+), 126.5 (d, J = 7.9 Hz, +, 2C), 125.8 (+, 2C), 115.9 (d, J = 21.4 Hz, +, 2C), 75.8 (+), 59.1 (+), 50.7 (−), 50.5 (−), 34.5, 22.7 (−). HRMS (TOF ES): found 410.1529, calculated for $C_{25}H_{22}FNO_2Na$ (M + Na) 410.1532 (0.7 ppm).

(−)-(1S,3S,4S,7S)-4,5-Dimethyl-3,7-diphenyl-2-oxa-5-azabicyclo-[5.1.0]octan-6-one (25a).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride (32) (378 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-1-phenylcyclo-prop-2-ene-1-carboxamide (**24a**) was used at the cyclization step as is without additional purification. To this end, amide **24a** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (3:2) as a colorless glass (R_f = 0.28). Yield 17.2 mg (0.056 mmol, 86%). $[\alpha]_D^{20}$ −55.3 (c = 0.80,

$CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.42−7.32 (m, 5H), 7.29−7.24 (m, 3H), 7.14−7.07 (m, 2H), 4.70 (dq, J = 10.8, 6.9 Hz, 1H), 4.38 (d, J = 10.8 Hz, 1H), 3.68 (dd, J = 6.4, 3.6 Hz, 1H), 3.08 (s, 3H), 1.71 (dd, J = 6.8, 3.5 Hz, 1H), 1.44 (t, J = 6.7 Hz, 1H), 1.12 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.5, 138.2, 136.6, 129.2 (+, 2C), 129.1 (+, 2C), 129.1 (+), 128.5 (+, 2C), 126.8 (+), 124.5 (+, 2C), 80.1 (+), 55.7 (+), 51.5 (+), 35.1, 27.6 (+), 23.4 (−), 15.1 (+). FTIR (NaCl, cm^{-1}): 1649, 1495, 1152. HRMS (TOF ES): found 330.1469, calculated for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470 (0.3 ppm).

(+)-(1R,3R,4R,7R)-4,5-Dimethyl-3,7-diphenyl-2-oxa-5-azabicyclo-[5.1.0]octan-6-one (ent-25a).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and (1*R*, 2*R*)-(−)-pseudoephedrine hydrochloride (*ent*-**32**) (378 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-1-phenylcyclo-prop-2-ene-1-carboxamide (*ent*-**24a**) was used at the cyclization step as is without additional purification. To this end, amide *ent*-**24a** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (3:2) as a colorless glass (R_f = 0.28). $[\alpha]_D^{20}$ +55.9 (c = 0.80, $CHCl_3$). Yield 17.6 mg (0.057 mmol, 88%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.41−7.32 (m, 5H), 7.30−7.25 (m, 3H), 7.14−7.10 (m, 2H), 4.70 (dq, J = 10.8, 7.0 Hz, 1H), 4.38 (d, J = 10.8 Hz, 1H), 3.68 (dd, J = 6.4, 3.5 Hz, 1H), 3.08 (s, 3H), 1.71 (dd, J = 6.9, 3.5 Hz, 1H), 1.44 (t, J = 6.7 Hz, 1H), 1.12 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.5, 138.2, 136.6, 129.2 (+, 2C), 129.1 (+, 2C), 129.1 (+), 128.5 (+, 2C), 126.8 (+), 124.5 (+, 2C), 80.1 (+), 55.7 (+), 51.5 (+), 35.1, 27.6 (+), 23.4 (−), 15.1 (+). FTIR (NaCl, cm^{-1}): 1645, 1495, 1152. HRMS (TOF ES): found 330.1467, calculated for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470 (0.9 ppm).

(−)-(1S,3S,4S,7S)-7-(4-Fluorophenyl)-4,5-dimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (25b).—This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride (32) (340 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude 1-(4-fluorophenyl)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylcycloprop-2-ene-1-carboxamide (**24b**) was used at the cyclization step as is without additional purification. To this end, amide **24b** (20 mg, 0.061 mmol) was treated with powdered KOH (6.8 mg, 0.122 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (3:1) as a colorless solid (R_f = 0.60, mp 73−75 °C). $[\alpha]_D^{20}$ −49.5 (c = 0.80, $CHCl_3$). Yield 18.6 mg (0.057 mmol, 93%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 (dd, J = 5.7, 1.6 Hz, 3H), 7.26 (s, 2H), 7.12−7.03 (m, 4H), 4.67 (dq, J = 10.8, 6.9 Hz, 1H), 4.38 (d, J = 10.8 Hz, 1H), 3.64 (dd, J = 6.5, 3.5 Hz, 1H), 3.07 (s, 3H), 1.70 (dd, J = 6.9, 3.5 Hz, 1H), 1.38 (t, J = 6.7 Hz, 1H), 1.14 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.4, 161.8 (d, J = 245.6 Hz), 136.4, 133.9 (d, J = 3.0 Hz), 129.2 (+, 2C), 129.1 (+), 128.4 (+, 2C), 126.2 (d, J = 8.0 Hz, +, 2C), 116.1 (d, J = 21.4 Hz, +, 2C), 80.0 (+), 55.4 (+), 51.5 (+), 34.6, 27.6 (+), 23.3 (−), 15.1 (+). FTIR (NaCl, cm^{-1}): 1648, 1510, 1232, 1151. HRMS (TOF ES): found 348.1383, calculated for $C_{20}H_{20}FNO_2Na$ (M + Na) 348.1376 (2.0 ppm).

(+)-(1R,3R,4R,7R)-7-(4-Fluorophenyl)-4,5-dimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (ent-25b).—This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (**14b**) (200 mg, 1.12 mmol, 1.0 equiv) and (1*R*,2*R*)-(−)-pseudoephedrine hydrochloride (*ent*-**32**) (340 mg, 1.68 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude 1-(4-fluorophenyl)-N-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylcycloprop-2-ene-1-carboxamide (*ent*-**24b**) was used at the cyclization step as is without additional purification. To this end, amide *ent*-**24b** (20 mg, 0.061 mmol) was treated with powdered KOH (6.8 mg, 0.122 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.14, mp 74−76 °C). $[\alpha]_D^{20}$ +50.3 (c = 0.90, $CHCl_3$). Yield 19.2 mg (0.059 mmol, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43−7.35 (m, 3H), 7.28−7.24 (m, 2H), 7.12− 7.02 (m, 4H), 4.67 (dq, *J* = 10.8, 7.0 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 3.64 (dd, *J* = 6.4, 3.5 Hz, 1H), 3.07 (s, 3H), 1.69 (dd, *J* = 6.9, 3.5 Hz, 1H), 1.38 (t, *J* = 6.7 Hz, 1H), 1.13 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.4, 161.8 (d, *J* = 245.6 Hz), 136.4, 133.9 (d, *J* = 3.1 Hz), 129.2 (+, 2C), 129.1 (+), 128.4 (+, 2C), 126.2 (d, *J* = 7.8 Hz, +, 2C), 116.1 (d, *J* = 21.6 Hz, +, 2C), 80.0 (+), 55.4 (+), 51.5 (+), 34.6, 27.6 (+), 23.3 (−), 15.1 (+). FTIR (NaCl, cm^{-1}): 1647, 1510, 1233, 1152. HRMS (TOF ES): found 348.1382, calculated for $C_{20}H_{20}FNO_2Na$ (M + Na) 348.1376 (1.7 ppm).

(−)-(1S,3S,4S,7S)-7-(2,4-Dichlorophenyl)-4,5-dimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (25c).—This compound was synthesized according to the typical procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**14c**) (200 mg, 0.87 mmol, 1.0 equiv) and (1*S*,2*S*)-(+)-pseudoephedrine hydro-chloride (32) (264 mg, 1.31 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude 1-(2,4-dichlorophenyl)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-N-methylcycloprop-2-ene-1-carboxamide (**24c**) was used at the cyclization step as is without additional purification. To this end, amide **24c** (20 mg, 0.053 mmol) was treated with powdered KOH (5.9 mg, 0.106 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.54, mp 144−146 °C). Yield 16.4 mg (0.043 mmol, 82%). $[\alpha]_D^{20}$ −85.2 (c = 0.70, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.5 Hz, 1H), 7.48−7.40 (m, 5H), 7.39 (d, *J* = 2.3 Hz, 1H), 7.28−7.24 (m, 1H), 5.16 (dq, *J* = 10.8, 7.0 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 4.22 (dd, *J* = 6.3, 3.2 Hz, 1H), 2.99 (s, 3H), 1.69 (dd, *J* = 6.7, 3.2 Hz, 1H), 1.54 (t, *J* = 6.5 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 170.8, 136.9, 134.1, 133.8, 133.7, 132.2 (+), 131.2 (+), 129.2 (+, 2C), 129.1 (+), 128.5 (+, 2C), 127.6 (+), 80.1 (+), 53.6 (+), 51.3 (+), 34.6, 27.9 (+), 22.3 (−), 15.1 (+). FTIR (NaCl, cm^{-1}): 1653, 1471, 1251, 1155. HRMS (TOF ES): found 376.0854, calculated for $C_{20}H_{20}Cl_2NO_2$ (M + H) 376.0871 (4.5 ppm).

(+)-(1R,3R,4R,7R)-7-(2,4-Dichlorophenyl)-4,5-dimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (ent-25c).—This compound was synthesized according to the typical procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (14c) (200 mg, 0.87 mmol, 1.0 equiv) and (1*R*,2*R*)-(−)-pseudoephedrine hydrochloride (*ent*-**32**) (264 mg, 1.31 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude 1-(2,4-dichlorophenyl)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylcycloprop-2-ene-1-carboxamide (*ent*-**24c**) was used at the cyclization step as is

without additional purification. To this end, amide *ent*-**24c** (20 mg, 0.053 mmol) was treated with powdered KOH (5.9 mg, 0.106 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.54, mp 140−141 °C). Yield 16.8 mg (0.045 mmol, 84%). $[\alpha]_D^{20}$ +81.8 (c = 0.70, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 8.5 Hz, 1H), 7.47−7.40 (m, 5H), 7.39 (d, J = 2.3 Hz, 1H), 7.30−7.24 (m, 1H), 5.16 (dq, J = 10.9, 7.0 Hz, 1H), 4.38 (d, J = 10.8 Hz, 1H), 4.22 (dd, J = 6.3, 3.1 Hz, 1H), 2.99 (s, 3H), 1.69 (dd, J = 6.7, 3.2 Hz, 1H), 1.54 (t, J = 6.5 Hz, 1H), 1.18 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 170.8, 136.9, 134.1, 133.8, 133.7, 132.2 (+), 131.2 (+), 129.2 (+, 2C), 129.1 (+), 128.5 (+, 2C), 127.6 (+), 80.0 (+), 53.6 (+), 51.3 (+), 34.6, 27.9 (+), 22.3 (−), 15.1 (+). FTIR (NaCl, cm^{-1}): 1653, 1474, 1253, 1152. HRMS (TOF ES): found 398.0702, calculated for $C_{20}H_{19}Cl_2NO_2Na$ (M + Na) 398.0691 (2.8 ppm).

(−)-(1S,3S,4S,7S)-4,5-Dimethyl-7-(naphthalen-1-yl)-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (25d).—This compound was synthesized according to the typical procedure from 1-(naphthalen-1-yl)cycloprop-2-ene-1-carboxylic acid (14d) (200 mg, 0.95 mmol, 1.0 equiv) and (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride (**32**) (288 mg, 1.43 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-N-methyl-1-(naphthalen-1-yl)cycloprop-2-ene-1-carboxamide (**24d**) was used at the cyclization step as is without additional purification. To this end, amide **24d** (20 mg, 0.056 mmol) was treated with powdered KOH (6.3 mg, 0.112 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.30, mp 217−220 °C). Yield 16.2 mg (0.045 mmol, 81%). $[\alpha]_D^{20}$ −115.1 (c = 0.70, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 9.30 (dd, J = 8.6, 1.0 Hz, 1H), 7.86−7.80 (m, 2H), 7.72 (dd, J = 7.1, 1.1 Hz, 1H), 7.67−7.61 (m, 3H), 7.57−7.44 (m, 5H), 5.55 (dq, J = 10.8, 7.0 Hz, 1H), 4.48 (d, J = 10.8 Hz, 1H), 3.96 (dd, J = 6.3, 2.8 Hz, 1H), 2.95 (s, 3H), 1.84 (dd, J = 6.3, 2.8 Hz, 1H), 1.23 (d, J = 7.0 Hz, 3H), 1.20 (t, J = 6.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 170.8, 137.3, 134.7, 134.6, 133.6, 129.4 (+, 2C), 129.1 (+), 128.9 (+), 128.5 (+, 2C), 128.2 (+), 127.6 (+), 126.5 (+), 126.5 (+), 125.4 (+), 124.9 (+), 80.0 (+), 52.4 (+), 51.0 (+), 34.1, 27.9 (+), 21.6 (−), 15.3 (+). FTIR (NaCl, cm^{-1}): 1645, 1391, 1152. HRMS (TOF ES): found 380.1638, calculated for $C_{24}H_{23}NO_2Na$ (M + Na) 380.1626 (3.2 ppm).

(+)-(1R,3R,4R,7R)-4,5-Dimethyl-7-(naphthalen-1-yl)-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (ent-25d).—This compound was synthesized according to the typical procedure from 1-(naphthalen-1-yl)cycloprop-2-ene-1-carboxylic acid (14d) (200 mg, 0.95 mmol, 1.0 equiv) and (1*R*,2*R*)-(−)-pseudoephedrine hydrochloride (*ent*-**32**) (288 mg, 1.43 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-1-(naphthalen-1-yl)cycloprop-2-ene-1-carboxamide (*ent*-**24d**) was used at the cyclization step as is without additional purification. To this end, amide ent-**24d** (20 mg, 0.056 mmol) was treated with powdered KOH (6.3 mg, 0.112 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.30, mp 222−224 °C). Yield 16.8 mg (0.047 mmol, 84%). $[\alpha]_D^{20}$ +118.5 (c = 0.70, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 9.30 (dd, J = 8.6, 1.1 Hz, 1H), 7.87−7.78 (m, 2H), 7.72 (dd, J = 7.2, 1.2 Hz, 1H),

7.69−7.60 (m, 3H), 7.58− 7.44 (m, 5H), 5.55 (dq, J = 10.9, 7.0 Hz, 1H), 4.48 (d, J = 10.8 Hz, 1H), 3.96 (dd, J = 6.3, 2.8 Hz, 1H), 2.95 (s, 3H), 1.84 (dd, J = 6.2, 2.8 Hz, 1H), 1.23 (d, J = 7.0 Hz, 3H), 1.20 (t, J = 6.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 170.8, 137.3, 134.7, 134.6, 133.6, 129.4 (+, 2C), 129.1 (+), 128.9 (+), 128.5 (+, 2C), 128.2 (+), 127.6 (+), 126.5 (+), 126.5 (+), 125.4 (+), 124.9 (+), 80.0 (+), 52.4 (+), 51.0 (+), 34.1, 27.9 (+), 21.6 (−), 15.3 (+). FTIR (NaCl, cm^{-1}): 1645, 1392, 1151. HRMS (TOF ES): found 380.1608, calculated for $C_{24}H_{23}NO_2Na$ (M + Na) 380.1624 (4.7 ppm).

(+)-(1S,3R,4S,7S)-4,5-Dimethyl-3,7-diphenyl-2-oxa-5-azabicyclo-[5.1.0]octan-6-one (28a).—This compound was synthesized according to the typical procedure from 1-phenylcycloprop-2-ene-1-carboxylic acid (**14a**) (200 mg, 1.25 mmol, 1.0 equiv) and (1*R*, 2*S*)-(−)-ephedrine hydrochloride (**33**) (378 mg, 1.88 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude *N*-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-1-phenylcycloprop-2-ene-1-carboxamide (**27a**) was used at the cyclization step as is without additional purification. To this end, amide **27a** (20 mg, 0.065 mmol) was treated with powdered KOH (7.3 mg, 0.13 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (3:2) as a colorless glass (R_f = 0.28). $[\alpha]_D^{20}$ +77.0 (c = 0.70, $CHCl_3$). Yield 16.8 mg (0.055 mmol, 84%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.36−7.29 (m, 5H), 7.27−7.19 (m, 3H), 7.08−7.03 (m, 2H), 4.64 (qd, J = 7.2, 4.2 Hz, 1H), 4.51 (d, J = 4.3 Hz, 1H), 3.62 (dd, J = 6.2, 3.4 Hz, 1H), 2.70 (s, 3H), 1.89 (dd, J = 7.0, 3.4 Hz, 1H), 1.62 (t, J = 6.6 Hz, 1H), 1.08 (d, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 171.3, 138.2, 136.5, 129.0 (+, 2C), 128.6 (+), 128.2 (+, 2C), 127.8 (+, 2C), 126.8 (+), 124.6 (+, 2C), 81.2 (+), 59.4 (+), 52.3 (+), 35.1, 29.0 (+), 22.6 (−), 14.6 (+). FTIR (NaCl, cm^{-1}): 1648, 1497, 1170. HRMS (TOF ES): found 330.1484, calculated for $C_{20}H_{21}NO_2Na$ (M + Na) 330.1470 (4.2 ppm).

(+)-(1S,3R,4S,7S)-7-(2,4-Dichlorophenyl)-4,5-dimethyl-3-phenyl-2-oxa-5-azabicyclo[5.1.0]octan-6-one (28c).—This compound was synthesized according to the typical procedure from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (**14c**) (150 mg, 0.65 mmol, 1.0 equiv) and (1*R*,2*S*)-(−)-ephedrine (**33**) (198 mg, 0.98 mmol, 1.5 equiv). After extraction and filtration through a silica plug crude 1-(2,4-dichlorophenyl)-*N*-((1*R*, 2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylcycloprop-2-ene-1-carboxamide (**27c**) was used at the cyclization step as is without additional purification. To this end, amide **27c** (60 mg, 0.16 mmol) was treated with powdered KOH (18 mg, 0.32 mmol). The product was isolated by column chromatography eluting with a hexane/EtOAc mixture (2:1) as a colorless solid (R_f = 0.26, mp 152−157 °C). Yield 52.2 mg (0.139 mmol, 87%). $[\alpha]_D^{20}$ +27.9 (c = 0.7, CHCl). ^{1} 3 H NMR (500 MHz, $CDCl_3$): δ 7.7 (d, J = 8.5 Hz, 1H), 7.4 (d, J = 2.3 Hz, 1H), 7.3−7.3 (m, 3H), 7.3−7.2 (m, 3H), 5.4−5.3 (m, 1H), 4.7 (d, J = 4.4 Hz, 1H), 4.3 (dd, J = 6.2, 3.1 Hz, 1H), 2.6 (s, 3H), 1.8 (dd, J = 6.6, 3.1 Hz, 1H), 1.5 (t, J = 6.4 Hz, 1H), 1.1 (d, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 170.8, 136.8, 133.9, 133.9, 133.9 (+), 133.9, 130.7 (+), 128.6 (+), 128.3 (+, 2C), 127.7 (+, 2C), 127.7 (+), 81.1 (+), 56.6 (+), 51.4 (+), 34.4, 29.5 (+), 22.9 (−), 14.3 (+). FTIR (NaCl, cm^{-1}): 1647, 1474, 1167. HRMS (TOF ES): found 398.0676, calculated for $C_{20}H_{19}Cl_2NO_2Na$ (M + Na) 398.0691 (3.8 ppm).

Supplementary Material

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17. In this report, we focused our efforts on diastereoselective studies of seven-membered rings only. Development of methods allowing for diastereoselective cyclization of larger rings is currently underway in our laboratories and will be reported in due course.

18. See Supporting Information for experimental details.

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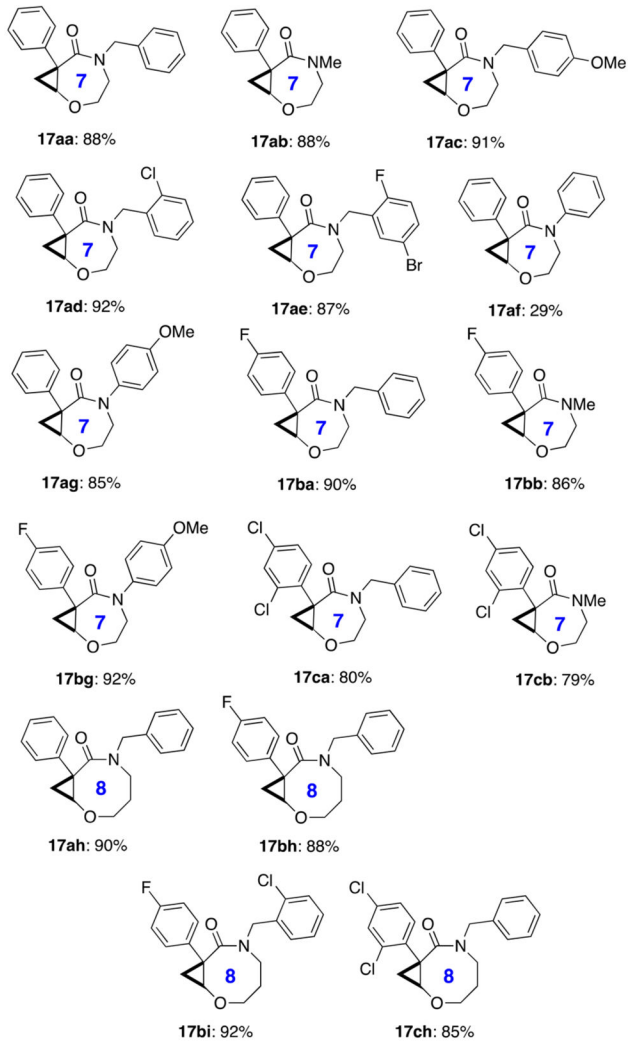


Figure 1.

Structures and yields of racemic cyclization products **17**. Yields of purified materials are provided.

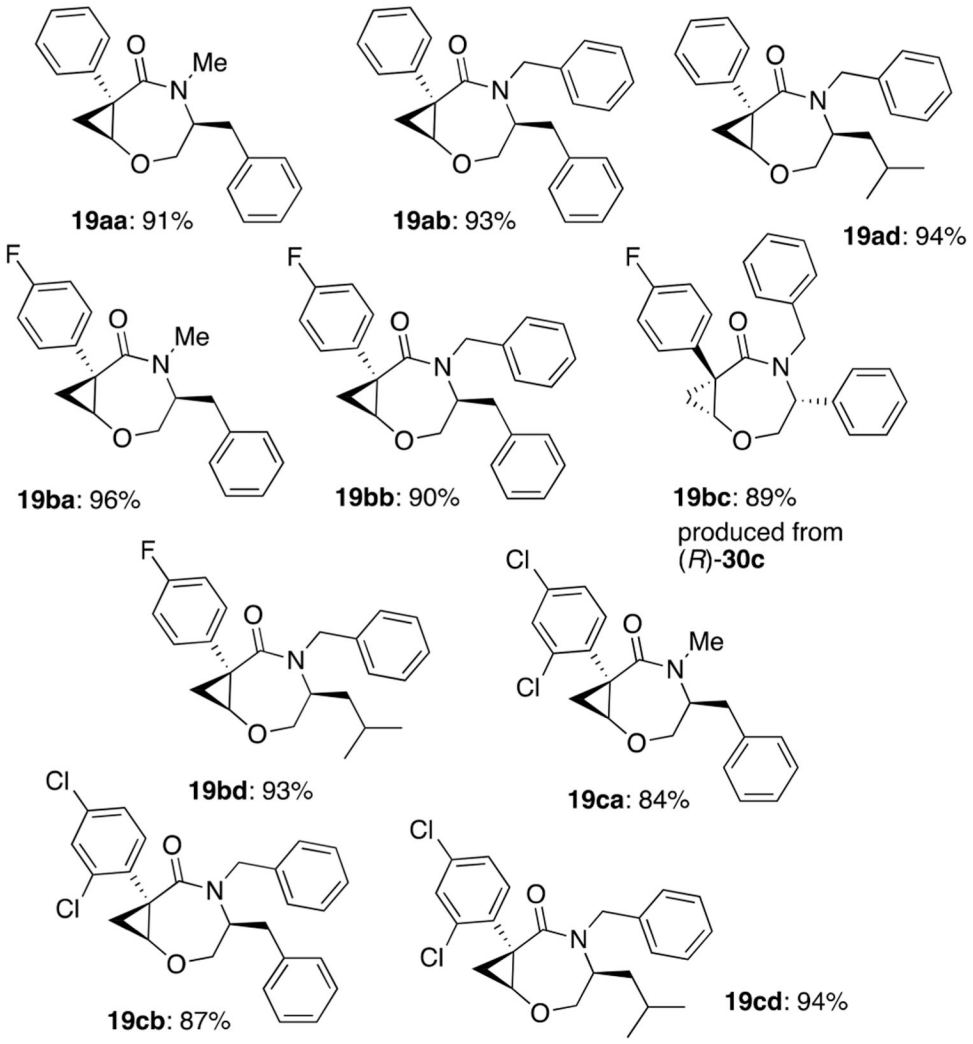


Figure 2.
Structures and yields of enantiopure cyclization products **19**. Yields of purified materials are provided.

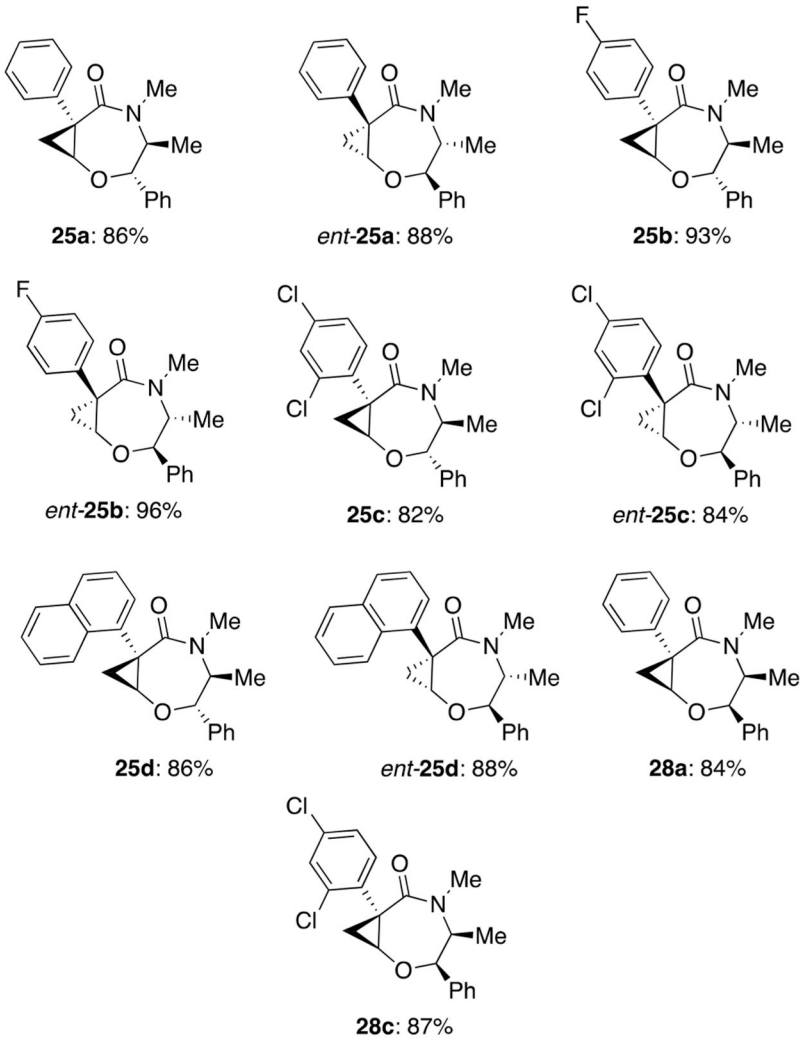
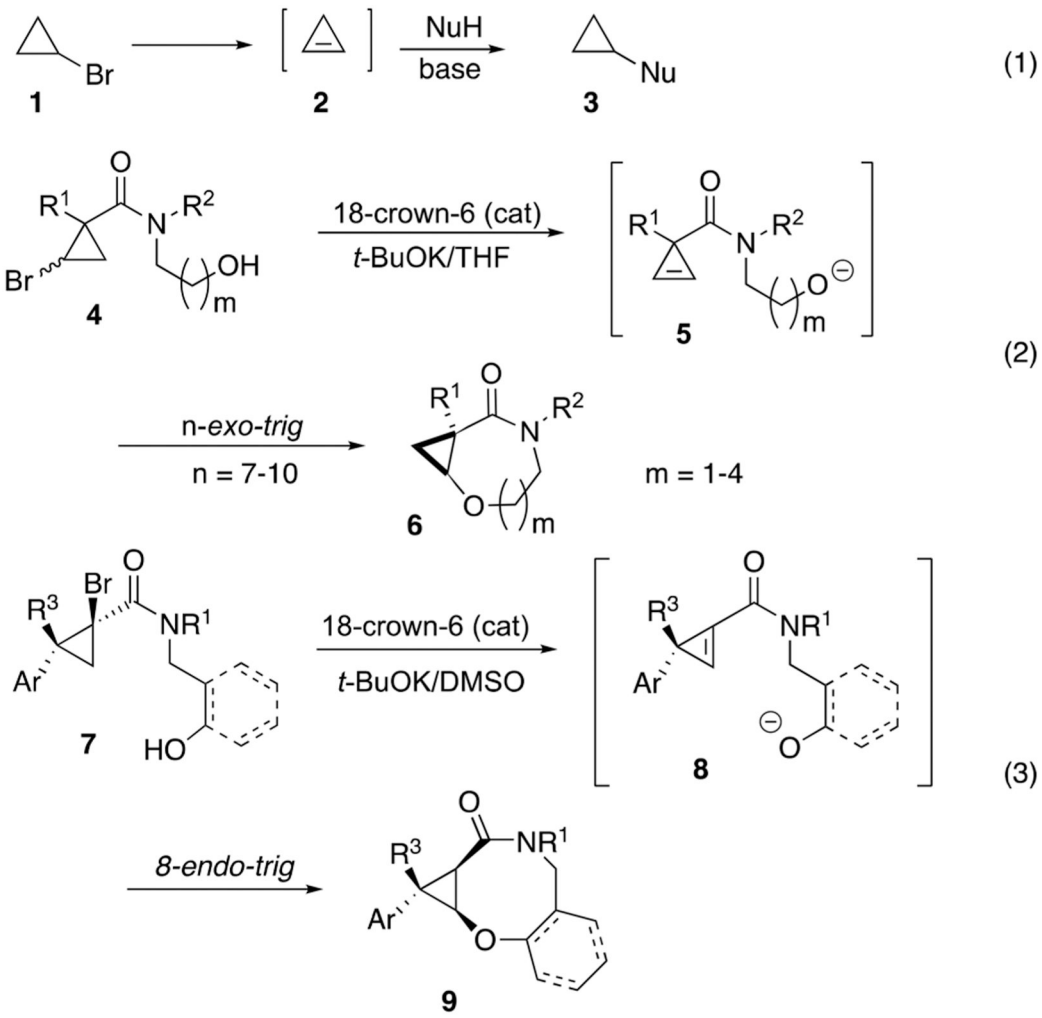
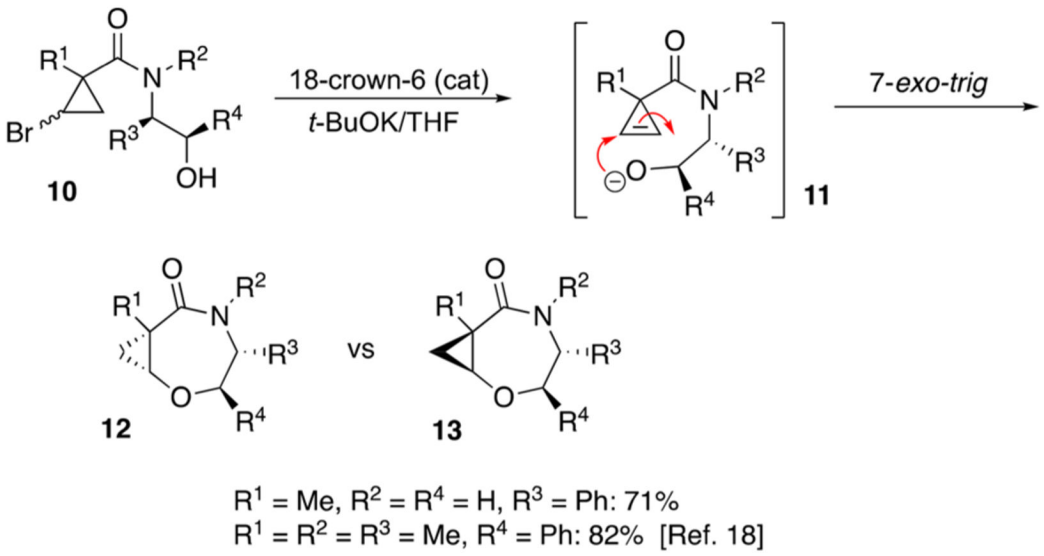


Figure 3.

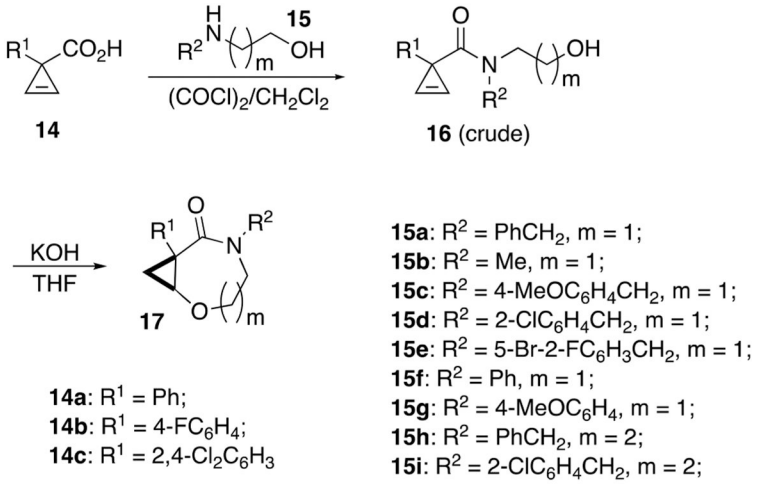
Structures and yields of chiral cyclization products **25** and **28**. Yields of purified materials are provided.



Scheme 1.



Scheme 2.



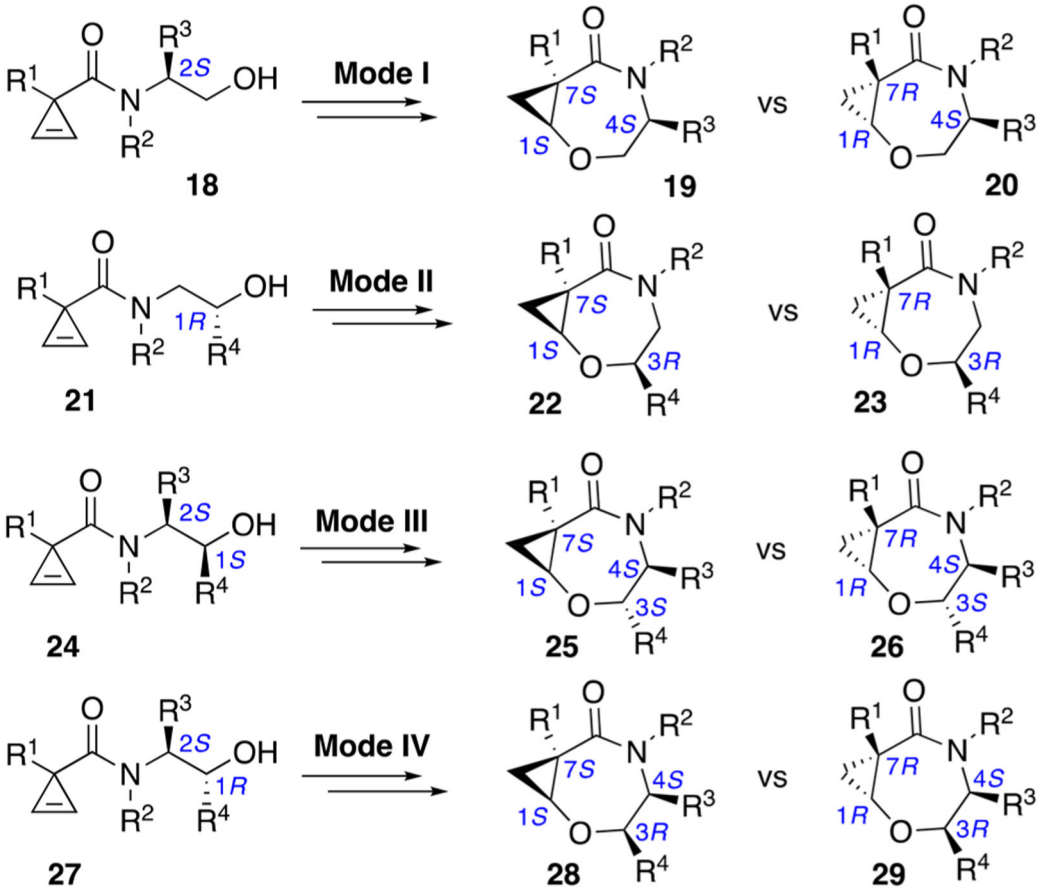
14a: R^1 = Ph;
14b: R^1 = 4-FC_6H_4;
14c: R^1 = 2,4-$Cl_2C_6H_3$

15a: R^2 = $PhCH_2$, m = 1;
15b: R^2 = Me, m = 1;
15c: R^2 = 4-$MeOC_6H_4CH_2$, m = 1;
15d: R^2 = 2-$ClC_6H_4CH_2$, m = 1;
15e: R^2 = 5-Br-2-$FC_6H_3CH_2$, m = 1;
15f: R^2 = Ph, m = 1;
15g: R^2 = 4-$MeOC_6H_4$, m = 1;
15h: R^2 = $PhCH_2$, m = 2;
15i: R^2 = 2-$ClC_6H_4CH_2$, m = 2;

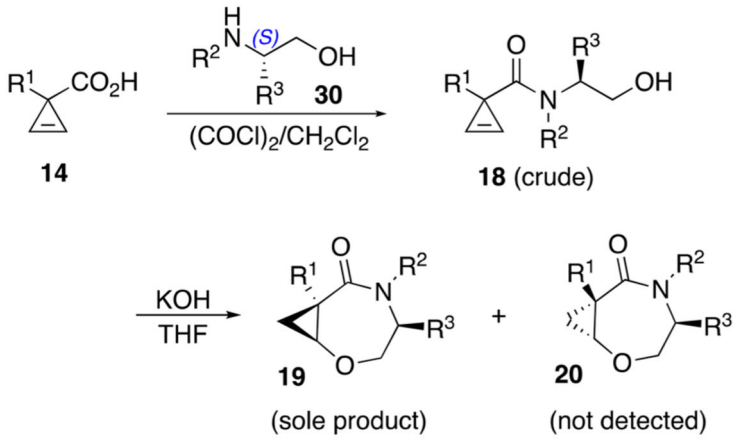
16aa, **17aa**: R^1 = Ph, R^2 = $PhCH_2$, m = 1;
16ab, **17ab**: R^1 = Ph, R^2 = Me, m = 1;
16ac, **17ac**: R^1 = Ph, R^2 = 4-$MeOC_6H_4CH_2$, m = 1;
16ad, **17ad**: R^1 = Ph, R^2 = 2-$ClC_6H_4CH_2$, m = 1;
16ae, **17ae**: R^1 = Ph, R^2 = 5-Br-2-$FC_6H_3CH_2$, m = 1;
16af, **17af**: R^1 = R^2 = Ph, m = 1;
16ag, **17ag**: R^1 = Ph, R^2 = 4-$MeOC_6H_4$, m = 1;
16ba, **17ba**: R^1 = 4-FC_6H_4, R^2 = $PhCH_2$, m = 1;
16bb, **17bb**: R^1 = 4-FC_6H_4, R^2 = Me, m = 1;
16bg, **17bg**: R^1 = 4-FC_6H_4, R^2 = 4-$MeOC_6H_4$, m = 1;
16ca, **17ca**: R^1 = 2,4-$Cl_2C_6H_3$, R^2 = $PhCH_2$, m = 1;
16cb, **17cb**: R^1 = 2,4-$Cl_2C_6H_3$, R^2 = Me, m = 1;

16ah, **17ah**: R^1 = Ph_4, R^2 = $PhCH_2$, m = 2;
16bh, **17bh**: R^1 = 4-FC_6H_4, R^2 = $PhCH_2$, m = 2;
16bi, **17bi**: R^1 = 4-FC_6H_4, R^2 = 2-$ClC_6H_4CH_2$, m = 2;
16ch, **17ch**: R^1 = 2,4-$Cl_2C_6H_3$, R^2 = $PhCH_2$, m = 2

Scheme 3.



Scheme 4.

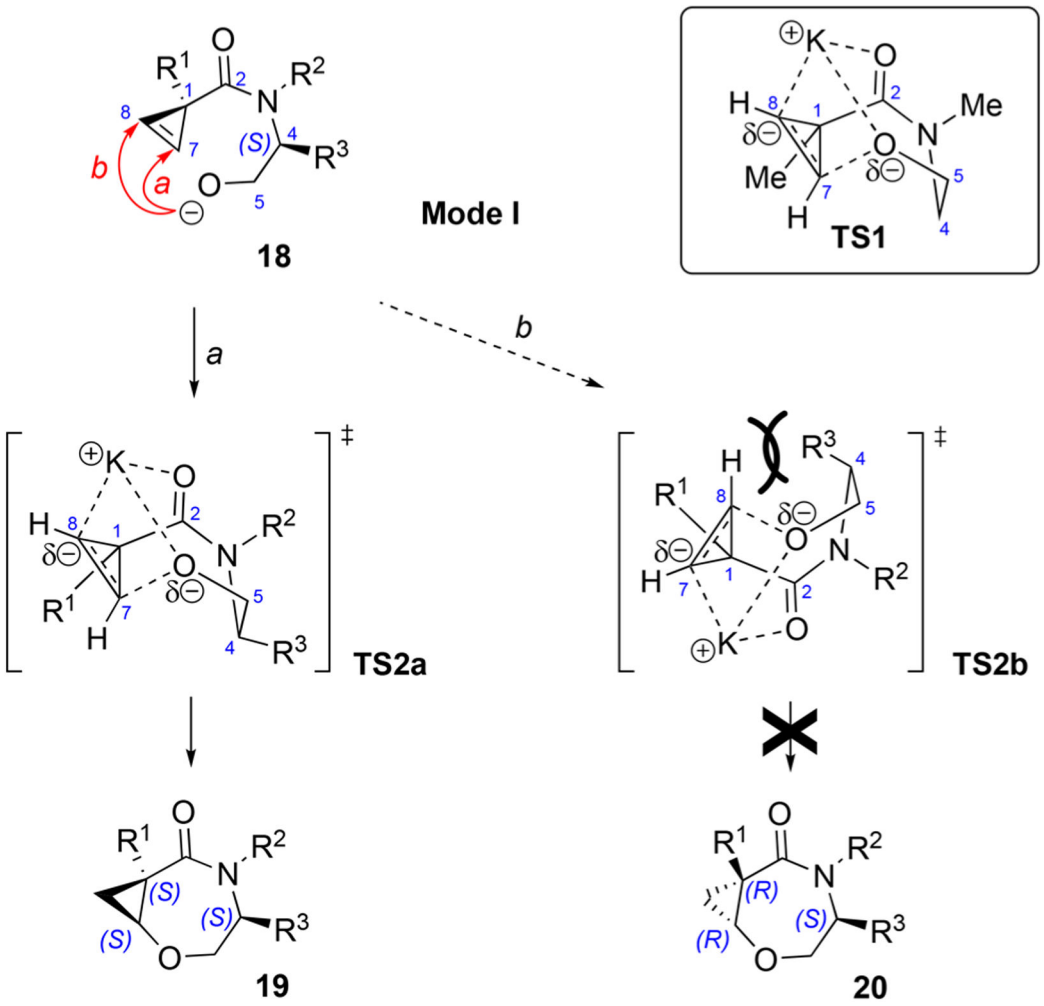


14a: R^1 = Ph;
14b: R^1 = 4-FC_6H_4;
14c: R^1 = 2,4-$Cl_2C_6H_3$

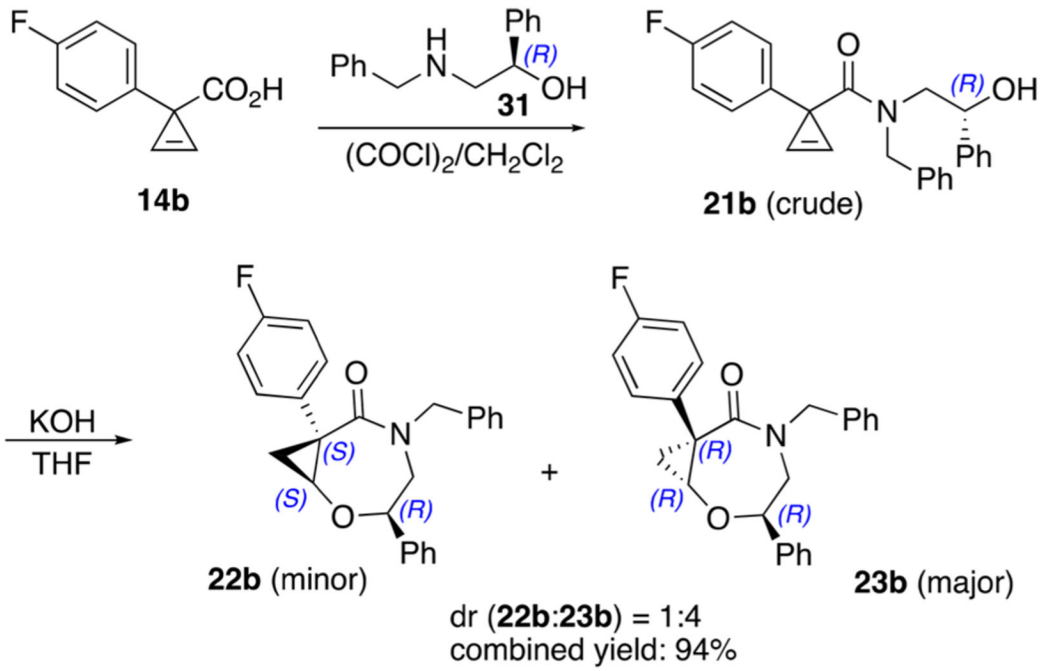
30a: R^2 = Me, R^3 = $PhCH_2$;
30b: R^2 = R^3 = $PhCH_2$;
30c: R^2 = $PhCH_2$, R^3 = Ph
(*R*)-isomer was employed;
30d: R^2 = $PhCH_2$, R^3 = Me_2CHCH_2

18aa, **19aa**, **20aa**: R^1 = Ph, R^2 = Me, R^3 = $PhCH_2$;
18ab, **19ab**, **20ab**: R^1 = Ph, R^2 = R^3 = $PhCH_2$;
18ad, **19ad**, **20ad**: R^1 = Ph, R^2 = $PhCH_2$, R^3 = Me_2CHCH_2;
18ba, **19ba**, **20ba**: R^1 = 4-FC_6H_4, R^2 = Me, R^3 = $PhCH_2$;
18bb, **19bb**, **20bb**: R^1 = 4-FC_6H_4, R^2 = R^3 = $PhCH_2$;
18bc, **19bc**, **20bc**: R^1 = 4-FC_6H_4, R^2 = $PhCH_2$, R^3 = Ph;
18bd, **19bd**, **20bd**: R^1 = 4-FC_6H_4, R^2 = $PhCH_2$, R^3 = Me_2CHCH_2;
18ca, **19ca**, **20ca**: R^1 = 2,4-$Cl_2C_6H_3$, R^2 = Me, R^3 = $PhCH_2$;
18cb, **19cb**, **20cb**: R^1 = 2,4-$Cl_2C_6H_3$, R^2 = R^3 = $PhCH_2$;
18cd, **19cd**, **20cd**: R^1 = 2,4-$Cl_2C_6H_3$, R^2 = $PhCH_2$, R^3 = Me_2CHCH_2

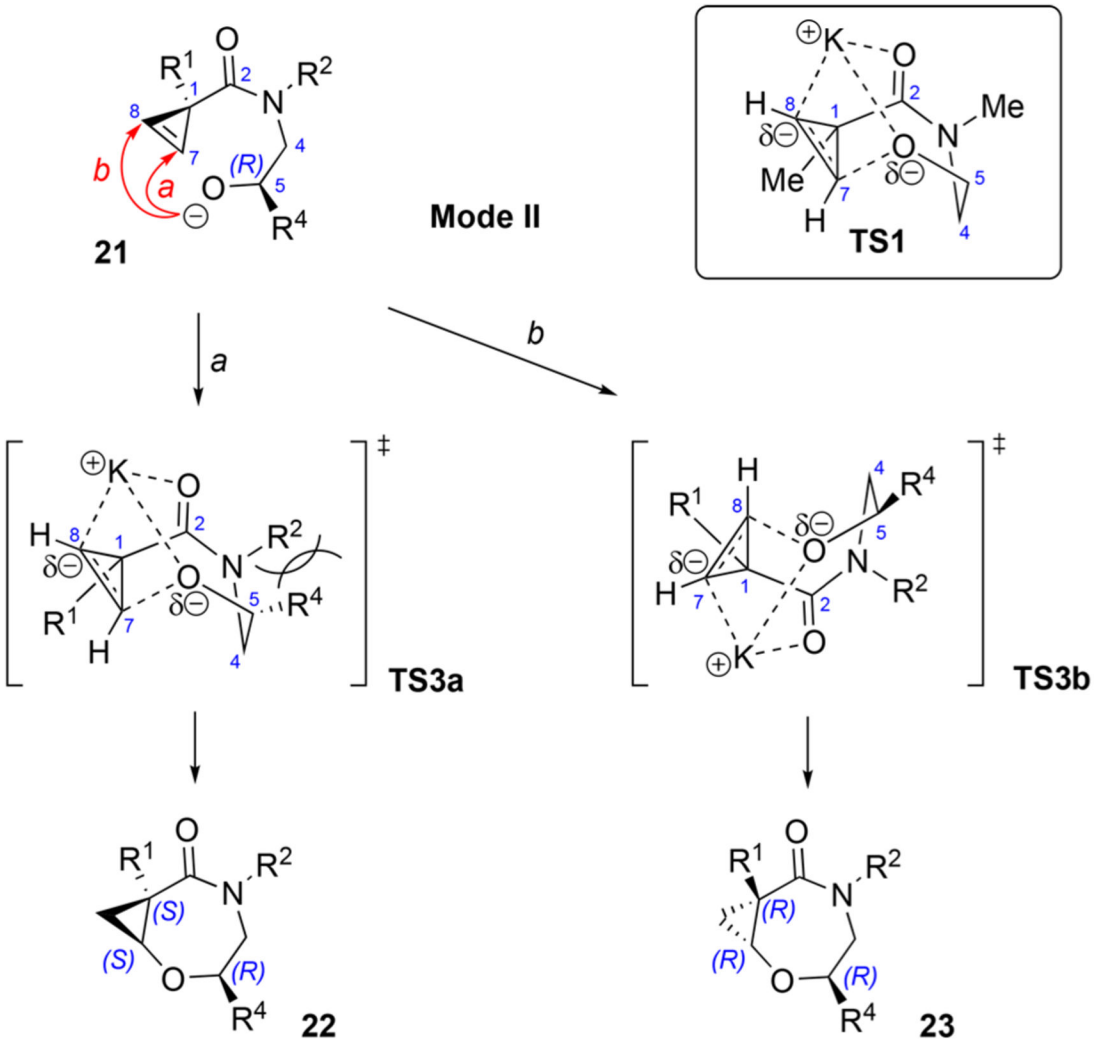
Scheme 5.



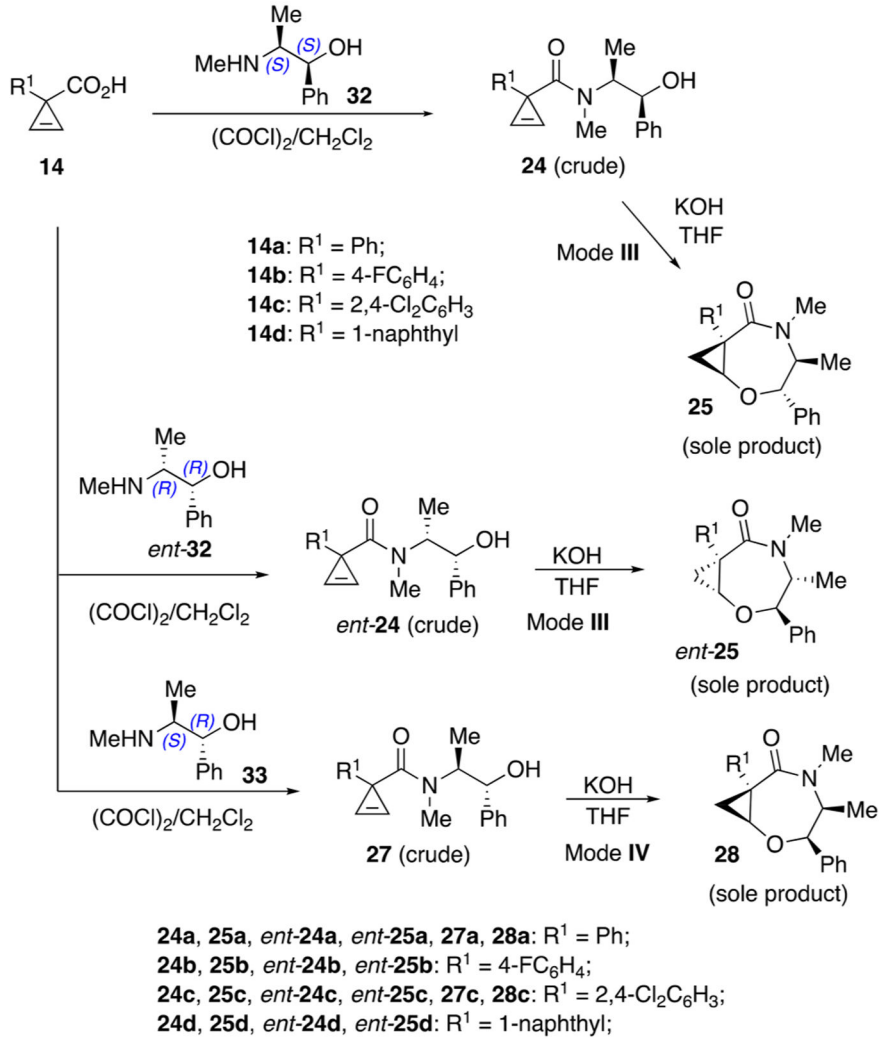
Scheme 6.



Scheme 7.



Scheme 8.



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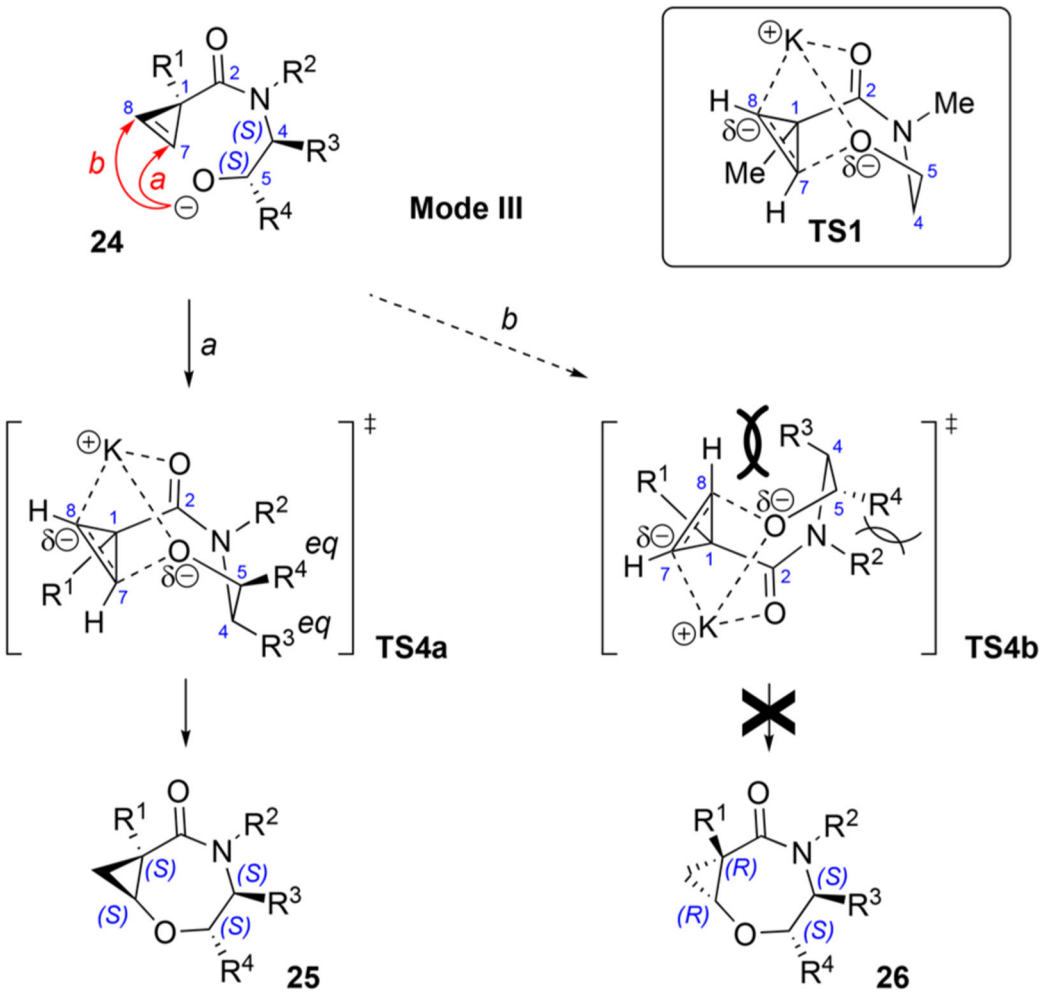
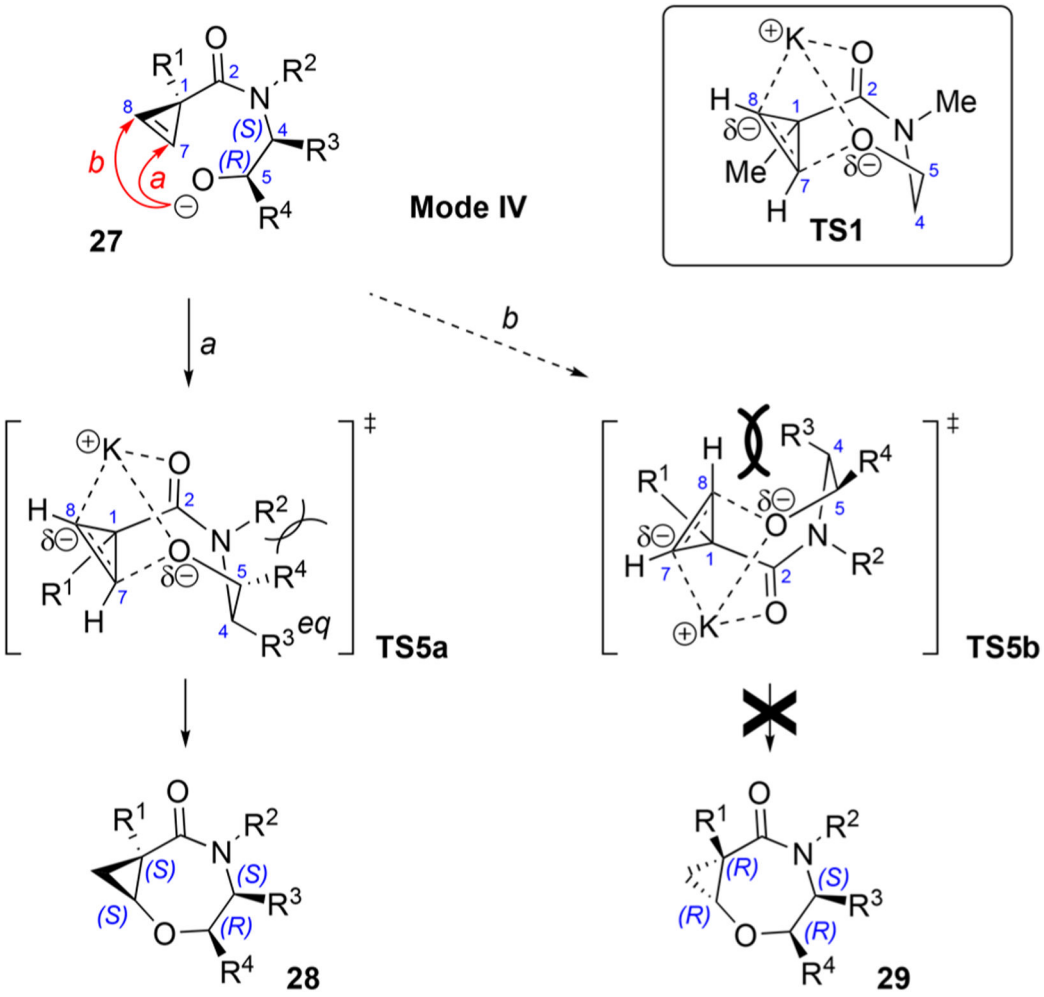


Scheme 10.



Scheme 11.

Table 1.

Biological Activities of 2-Oxa-5-azabicyclo[5.1.0]octan-6-ones

	MIC, μM *M. abscessus*	**IC_{50}, μM *M. abscessus***	**IC_{50}, μM HeLa**
19aa	100 ± 6.5	N/A	>100
19ab	50 ± 10.6	6.25 ± 0.07	79.9 ± 8.5
19ba	>100	>100	>100
19bb	50 ± 2.3	3.13 ± 0.04	85.1 ± 4.9
19ca	100 ± 3.8	25.4 ± 3.0	>100
19cb	>100	N/A	>100
25a	>100	>100	>100
ent-25a	>100	>100	>100
25d	>100	>100	103.2 ± 19.4
28a	>100	>100	>100